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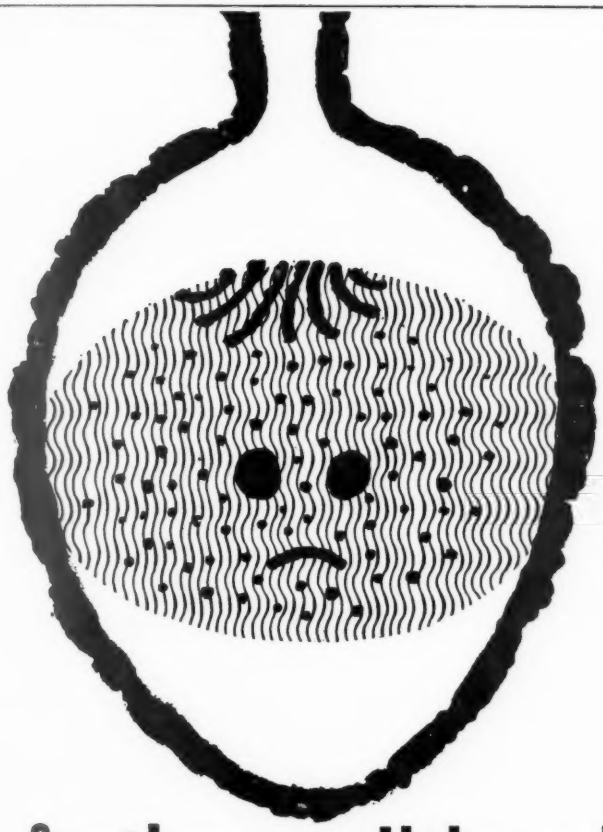

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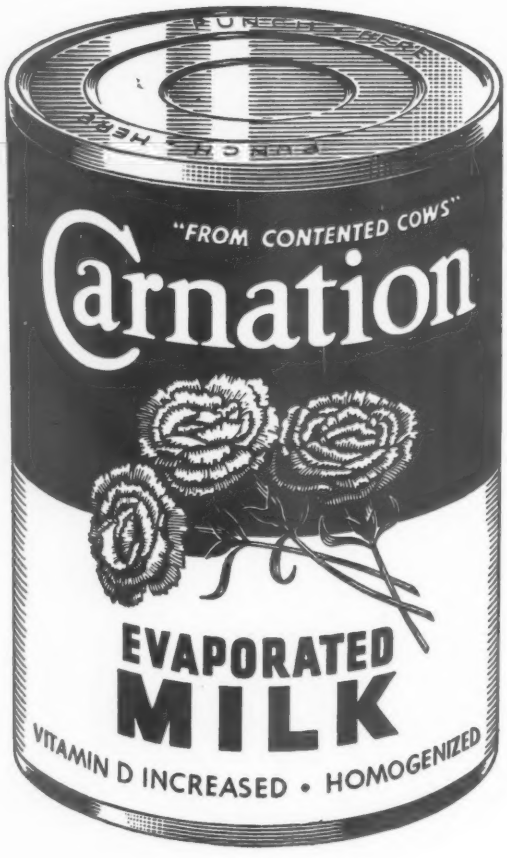

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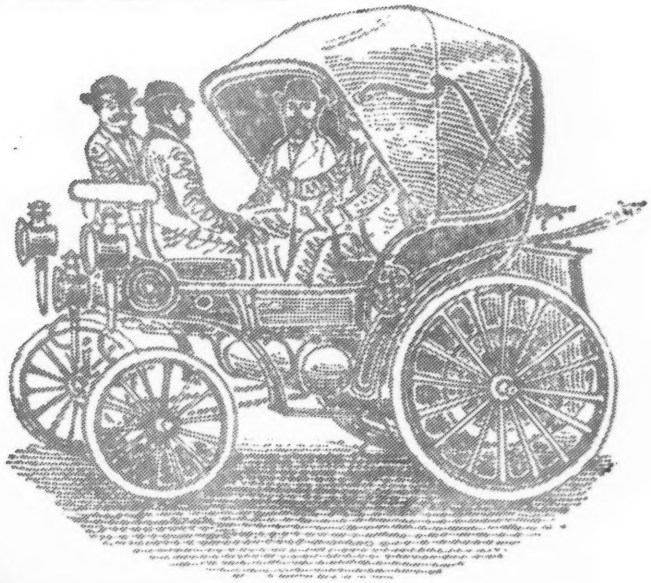

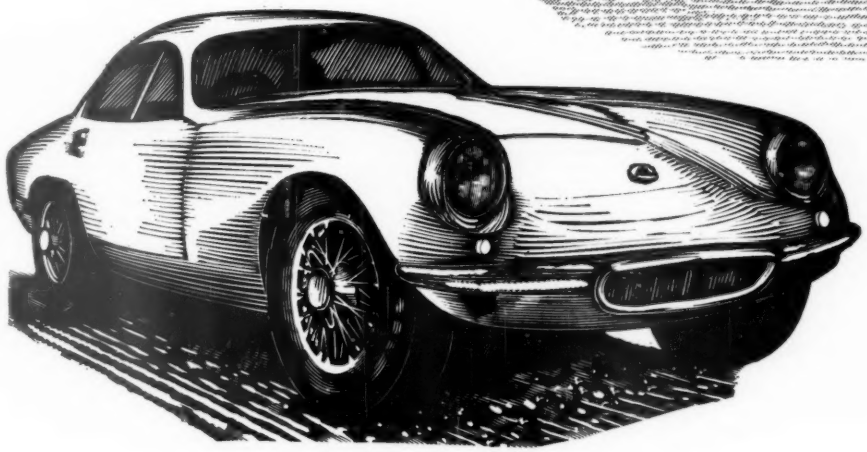

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9 GALACTOSAEMIA (W)
10 GASTRO-INTESTINAL DISORDERS (J, K, V)
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13 MALNUTRITION (O)
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15 MILK MODIFICATION (O, R)
16 NORMAL FEEDING (A, B, G, I, L, N)
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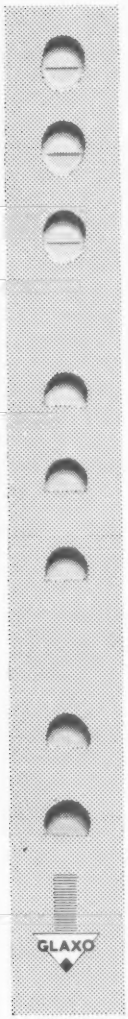

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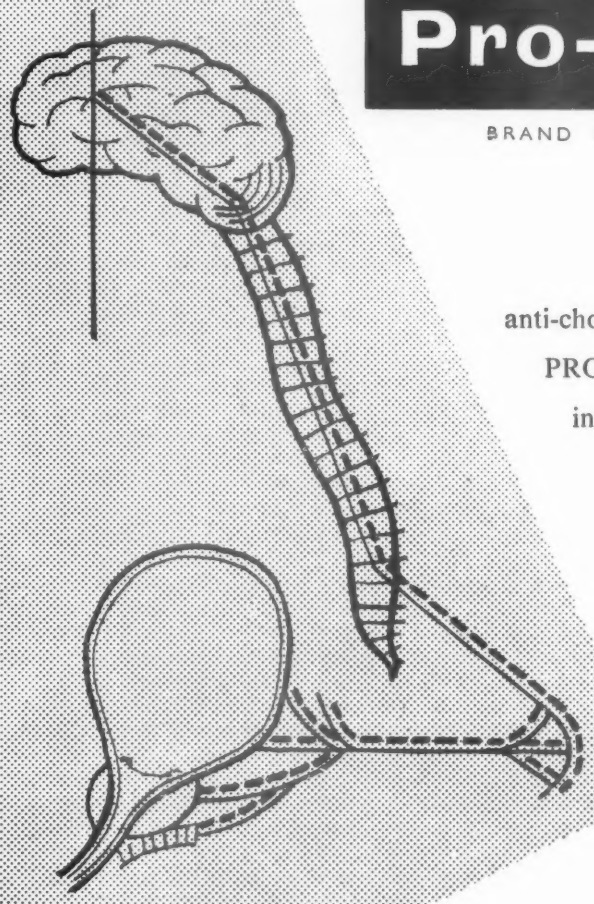

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HYPOPLASTIC ANAEMIA IN INFANCY AND CHILDHOOD: ERYTHROID HYPOPLASIA

BY

D. W. O'GORMAN HUGHES

From the Royal Alexandra Hospital for Children, Sydney, Australia

(RECEIVED FOR PUBLICATION JULY 7, 1960)

In 1936, Josephs reported 'a hypoplastic or aplastic type of anaemia confined to a failure of erythropoiesis' in two children. Diamond and Blackfan (1938) gave a more detailed description of the disorder in four children, and emphasized the features of a chronic progressive anaemia beginning early in infancy, with a tendency to moderate depression of the leucocyte and thrombocyte counts, and selective hypoplasia of the red cell precursors in the bone marrow. Several reports of this disease have appeared since (Rinvik, 1940; Kohlbry, 1941; Høyer, 1942; Rubell, 1942; Robson and Sweeney, 1948; Smith, 1949, 1953, 1959; Palmen and Vahlquist, 1950; Cathie, 1950; Lelong, Joseph, Polonowski, Desmonts and Colin, 1951; Anderson, 1952; Donnelly, 1953; Aldridge and Kidd, 1953; Kåss and Sundal, 1953; Verger and Leger, 1953; Fisher and Allen, 1953; Arrowsmith, Burris and Segaloff, 1953; Burgert, Kennedy and Pease, 1954; Diamond, 1954; Harper and Geikie, 1955; Calvert and Robson, 1956; Sundal, 1956; Pearson and Cone, 1957; Gasser, 1957), and a total of about 70 cases have been recorded. The reports have conformed to the original descriptions, with the exception that marrow examinations in some instances have revealed normal or increased numbers of normoblasts (Cathie, 1950). Various terms used to designate this haematological disorder include congenital hypoplastic anaemia, chronic hypoplastic anaemia (Josephs-Diamond-Blackfan type), erythrogenesis imperfecta, congenital pure red cell anaemia, chronic erythroblastopenia and pure red cell aplasia.

The aetiology is unknown, but is considered by many to rest in a congenital anomaly of the erythron, and the finding of associated congenital anomalies provides some support for this theory. The identification of anthranilic acid in the urine of some children with this disease suggested the presence of an inborn error of tryptophane metabolism; the administration of riboflavin to these patients resulted in a decrease in the excretion of anthranilic acid, but did not alter the haematological status (Altman and Miller, 1953). Smith (1949) reported the history of a child in whom anaemia developed in early infancy; the maternal antibody titre of anti:A was 1:128,000. It appears that isoimmunization may produce extreme and prolonged depression of the red cell precursors in infancy.

Erythroid hypoplasia, in more general terms, is of varied aetiology, and may occur at all ages. Acute hypoplasia may result from toxic, infective or allergic factors (Gasser, 1957), and sudden crises may develop in congenital spherocytosis (Owren, 1948), sickle cell anaemia (Chernoff and Josephson, 1951), and acquired haemolytic anaemia (Seip, 1955). Chronic forms of the disease have been attributed to chemical agents and autoimmune processes (Eisemann and Dameshek, 1954; Bonham Carter, Cathie and Gasser, 1954; Bousser, Christol, Dausset, Rampon, Jallut and Mery, 1955), and have been associated with the presence of thymic tumours. The subject of chronic erythroid hypoplasia in adults has been reviewed by Tsai and Levin (1957), but this report has included cases only where erythroid proportions were reduced in marrow examinations. Various forms of refractory anaemia with hypercellular bone marrow patterns have been described more recently by Dacie, Smith, White and Mollin (1959), and Vilter, Jarrold, Will, Mueller, Friedman and Hawkins (1960). In many instances the aetiology is unknown, and occasionally there have been reports, both in adults and children, of a familial incidence of the disease (Burgert *et al.*, 1954; Diamond, 1954; Loeb, Moore and Dubach, 1953; Wallman, 1956).

For some time effective therapy of erythroid hypoplasia in infancy and childhood was restricted to the frequent administration of blood transfusions, though spontaneous remissions were known to occur. Three of 12 children cited by Diamond underwent spontaneous remission. From 1953 onwards, reports have been published concerning the successful use of corticotrophin and cortico-

T
ERYTHROID HYPOPLASIA: CLINTURES

Case	1 N.G.	2 S.McK.	3a J.M.	3b J.M.	
Age when pallor first noted	4 months	? 2 months	18 months	9 ye: s 10 m	1 r
Age of first admission	11 months	4½ months	18 months		3 r
Sex	Male	Female	Male	Male	
Blood counts:					
Initially:					
Haemoglobin (g./100 ml.)	3·1	3·0	3·3	8·1	
Red cell count (× 10^6/c.mm.)	0·98	1·0	1·0	2·1	
Reticulocytes (× 10^3/c.mm.)			0	10	
%			0·0	<0·5	
Smear	Normocytic, normochromic	Normocytic, normochromic	Normocytic, normochromic	M acrocy slight	
Leucocytes (c.mm)		9,500	8,100	5,400	
Neutrophils (c.mm.)		5,400	2,000	2,500	
Thrombocytes (× 10^3/c.mm.)	Numerous	Numerous	318	330	Nu
Subsequent range:					
Leucocytes (× 10^3/c.mm.)	3·1–14	8·0–22	4·0–11	5·4–8·	5
Neutrophils (× 10^3/c.mm.)	2·1–9·2	3·8–11	1·2–4·7	2·5–4·	1
Thrombocytes (× 10^3/c.mm.)	80–500	130–260	320–440	380	
Maximum reticulocyte counts before steroid therapy (× 10^3/c.mm.)	<20	58	<50	<10	
Other investigations:					
Blood urea (mg./100 ml.)		27		28	
Direct Coombs' test				Negati	N
Serum bilirubin (mg./100 ml.)				<0·5	
Blood group: Patient	A Rh positive	A Rh positive	A Rh negative		B Rh
Mother		A Rh positive	O Rh positive		AB
Leucocyte chromatin pattern ..		Positive (F.)	Negative (M.)		
Physical features	Dwarfism; bilateral urinary malformation	Dwarfism; absence of sexual development; blue sclerae	Normal growth; inverted nipples		nthic ced wth

3a First admission to this hospital.

3b Relapse with megaloblastic features.

steroids in some patients, and these agents have now provided the mainstay of drug therapy in this disease. Arrowsmith *et al.* (1953) reported an unusual history of a child in whom megaloblastic erythropoiesis developed during steroid therapy, and normal erythropoiesis was obtained with the use of cortisone, folic acid and vitamin B_{12}. After splenectomy, cortisone and vitamin B_{12} therapy were required for some time to maintain a full haematological remission.

Present Investigation

The present series comprises eight patients with erythroid hypoplasia who developed anaemia within the first 18 months of life. All were admitted to the Royal Alexandra Hospital for Children, Sydney, between January 1953 and March 1960. The following criteria were required for inclusion in this report:

(1) A chronic aregenerative anaemia with relatively normal leucocyte and thrombocyte counts, appearing in the early months of life; (2) exclusion of cases if underlying systemic disease or postnatal physico-chemical hazards were considered to be of major aetiological significance. Bone marrow studies were performed on all eight patients, usually by aspiration from the iliac crest or tibia, and occasionally by means of bone trephine. In all smears, no abnormality of the myeloid cells or megakaryocytes was detected. The term 'erythroid hypoplasia' was used to signify a failure of maturation of adequate numbers of erythroid marrow cells to reticulocytes and erythrocytes, 'erythroblastic hypoplasia' being used more specifically to denote depression of the normoblasts to an arbitrary level of 10% or less of the total nucleated cells in the marrow. Defects in normoblastic maturation included multi-lobed and distorted nuclei, abnormal nuclear chromatin structure, scanty cytoplasm, and defective haemoglobinization of the nucleated red cells. Over the past three years, section of the clotted marrow specimen has been used as a guide to cellularity. With regard to earlier specimens, if it were considered that dilution with blood interfered with the correct interpretation, no comment concerning marrow cellularity was made.

TABLE I—CLINICAL FEATURES AND LABORATORY FINDINGS

	3b J.M.	4 C.J.	5 S.L.	6 K.W.	7 D.McC.	8 J.A.
Age	9 years 10 months	1 month 3 months	? 3 months	birth 2 months	2 weeks 5 months	3 months 5 months
Sex	Male	Male	Female	Female	Female	Female
Haemoglobin (g. per 100 ml.)	8·1 2·1	3·7 1·3	4·5 1·3	3·9 0·98	2·5 0·7	3·3
Red cells (millions per c.mm.)	10 <0·5	13 <0·5	40 3	13 <0·5	1 <0·5	
Blood picture	Macrocytic	Slight anisocytosis	Moderate anisocytosis	Moderate macrocytosis	Moderate macrocytosis	Normocytic, normochromic
White cells (per c.mm.)	5,400 2,500	17.000 5,600	13,000 4,200	7,000 4,000	11,000 3,900	8,000 6,300
Reticulocytes (per c.mm.)	330	Numerous	Numerous	240	210	Numerous
Serum bilirubin (mg. per 100 ml.)	5·4–8·6 2·5–4·6	5·0–14 1·2–8·7	7·0–19 2·2–14	7·0–10 1·7–6·1	8·0–22 2·8–13	5·0–8·0 1·2–6·3
Urobilinogen (mg. per 24 hours)	380	200	300	Numerous	190–760	130–360
Urea clearance (%)	<10	<15	53	<20	<10	30
Sugar tolerance test (mg. per 100 ml.)	28	34	36–52	22	22–44	22
Coombs' test	Negative	Negative	Negative	<0·5	Negative	Negative
Saline agglutinins (titre)	<0·5	<0·5	<0·5	<0·5	<0·5	<0·5
Blood group		B Rh positive AB Rh positive	A Rh positive O Rh positive	A Rh positive B Rh positive	O Rh positive O Rh positive	A Rh negative A Rh positive
Bone marrow		Positive (F.)	Positive (F.)	Positive (F.)		Positive (F.)
Physical abnormalities		Epicanthic folds; widely spaced eyes; normal growth	Dwarfism; webbed neck; exomphalos; inverted nipples widely spaced eyes	Small; epicanthic folds; wide fontanelle; widely spaced eyes; short neck	Dwarfism; wide fontanelle; blue sclerae	Dwarfism; skeletal abnormality; short neck; blue sclerae; inverted nipples

The significant clinical laboratory features are listed in Table 1. Bone marrow findings are summarized in Table 2.

Case Reports

Case 1. N.G., a male infant, was born in June 1943. Pallor was noted from the age of 4 months, and when 8 months old he received his first blood transfusion. He was admitted to this hospital at the age of 11 months, when a severe aregenerative orthochromic anaemia was detected. The child received 120 blood transfusions, representing a total of 82 litres of blood, over the ensuing 10 years, and at no stage did signs of red cell regeneration appear. Stunted growth was a prominent feature. Pyuria was detected from the age of 5 years onwards. Bone marrow examinations in 1945 and 1949 revealed extreme depression of the red cell precursors. The child died of renal failure in 1954, at the age of 11½ years. Autopsy revealed extensive haemosiderosis, gross hepatosplenomegaly, bilateral double ureters, congenital bilateral hydronephrosis and pyelonephritis, and a moderately hypocellular bone marrow with marked depression of the erythroid elements. No abnormality of the myeloid or megakaryocyte elements was detected.

Comment: The presence of erythroid hypoplasia in infancy and the urinary malformations suggest a common congenital origin. The duration of the anaemia should exclude the possibilities of azotaemia and chronic infection as major aetiological factors.

Case 2. S.McK., a female infant, was born on July 23, 1947. Transient jaundice developed on the fourth day of life. At the age of 4½ months she was admitted to this hospital with a severe normocytic normochromic anaemia, and between 1947 and 1958 she received 32 blood transfusions at intervals varying between 33 and 402 days. Her progress was consistent with that of an aregenerative anaemia with periodic remissions; during relapse reticulocytopenia was constantly noted. In 1958 steroids were administered in large doses (up to 48 mg. of methylprednisolone daily) for three weeks without haematological improvement. A blood transfusion was administered and methylprednisolone therapy was continued in a dose of 8 mg. daily for six months and 4 mg. daily for eight months. In January 1960, the haemoglobin value was 15 g. per 100 ml., and the child had not received a transfusion for 14 months. She was markedly dwarfed, her height being only 4 ft. 4 in. at the age of 12½ years. Bone marrow studies were performed on several occasions: in June 1948, erythroblastic hypoplasia was noted; in October 1958 (before administering steroid therapy), the erythroid proportions were normal, and defective normoblastic maturation and

TABLE 2

ERYTHROID HYPOPLASIA: BONE MARROW FINDINGS

Case	Date	Age yrs	Age mths	Method	Clinical Status	Cellularity	Myeloid: Erythroid Ratio	N.R.C. % Total	N.R.C. % Normoblasts	N.R.C. % Megaloblasts	Comments
1. N.G.	20.6.45	2		Trephine	Anaemia	Cellular					Erythroblastic hypoplasia
	15.3.49	6		Aspiration	Anaemia		69	1	1	—	Erythroblastic hypoplasia
	4.11.54	11	6	Section	Autopsy	Slightly hypocellular					Erythroblastic hypoplasia, haemosi erosis
2. S.McK.	24.6.48		11	Trephine	Anaemia	Cellular	12·4	5	5	—	Erythroblastic hypoplasia
	7.10.58	11	3	Aspiration	Anaemia	Cellular	3·5	18	18	—	Maturation defect; scanty cytoplas of la nucleated red cells; haemoside in-lade macrophages engulfing late nor noblas (erythrophagocytosis)
	16.12.58	11	5	Aspiration	Post transfusion; steroids	Cellular					Similar to previous aspirate
	16.1.60	12	6	Aspiration	Remission; steroids	Cellular	4	16	16	—	Normal erythroid proportions; rregul cytoplasm in some late nucleated red ce
3. J.M.	15.4.52	2	1	Aspiration	Anaemia	Cellular	4·6	14	14	—	Defective haemoglobinization and nucle distortion of late nucleated red cells
	4.5.53	3	2	Aspiration	Anaemia	Cellular	121	0·5	0·5	—	Erythroblastic hypoplasia
	21.2.58	7	11	Aspiration	Anaemia	Cellular	9·8	7	7	—	Erythroblastic hypoplasia
	8.1.60	9	10	Aspiration	Relapse; no steroids for four months	Cellular		5	4	1	Erythroblastic hypoplasia, abnormal nucle structure, some megaloblasts
	22.1.60	9	10	Aspiration	Steroids; Hb 9·3 g./100 ml.	Cellular	1	45	25	20	Numerous megaloblasts, defective norm blastic maturation
	4.2.60	9	11	Aspiration	Remission; steroids, folic acid, vitamin B_{12}	Cellular	1·8	31	29	2	Improvement; occasional megaloblasts, maturation of normoblasts less defective
4. G.J.	4.10.56		4	Aspiration	Anaemia		8	8·3	8·3	—	Erythroblastic hypoplasia
	8.8.57	1	2	Aspiration	Remission; steroids		2·7	22	22	—	Normal marrow
	23.10.58	2	4	Aspiration	Remission; steroids		4·6	13	13	—	Normal marrow
	14.1.60	4		Aspiration	Relapse	Cellular	3	21	21	—	Normal marrow
5. S.L.	1.6.56		5	Aspiration	Anaemia		2·5	17	17	—	Defective maturation of nucleated red cell numerous cells with minimal cytoplas resembling early nucleated red cells n included in count
	25.10.57	1	7	Aspiration	Anaemia	Cellular	2·4	29	29	—	Defective cytoplasm and nuclear maturatio difficult to determine stages of develo ment
	7.1.58	2		Aspiration	Remission; steroids	Cellular	2·3	24	24	—	Improvement
	14.1.60	4		Aspiration	Relapse; no steroids	Cellular	1·6	27	27	—	Normal marrow
6. K.W.	14.10.58	8 weeks		Aspiration	Anaemia		1·3	10	9	1	Erythroblastic hypoplasia, occasion megaloblasts
	20.10.58	9 weeks		Aspiration	Post transfusion		62	1			Erythroblastic hypoplasia, occasional megaloblasts, hypersegmentation of pol morphs
	5.12.58		4	Aspiration	Anaemia; folic acid	Cellular	4·6	6	5·5	0·5	Erythroblastic hypoplasia, occasion megaloblasts
	2.3.59		7	Aspiration	Anaemia; folic acid		21·5	2	2	—	Erythroblastic hypoplasia
7. D.McC.	22.10.58		5	Aspiration	Anaemia		56	1	1	—	Erythroblastic hypoplasia
	21.1.60	1	8	Aspiration	Remission; steroids	Cellular	1·9	29	29	—	Defective cytoplasm of some nucleated re cells
8. J.A.	4.2.60		5	Aspiration	Anaemia	Cellular	16	5	5	—	Erythroblastic hypoplasia
	23.3.60		6	Aspiration	Regression; steroids	Cellular		33	8	25	Marked megaloblastic changes; defecti maturation of other nucleated red cells
	1.4.60		6½	Aspiration	Regression; steroids	Cellular					Similar picture; numerous megaloblasts
	12.4.60		7	Aspiration	Remission; steroids, folic acid	Cellular		30	25	5	Only few megaloblasts; defective maturatio of nucleus and cytoplasm of man nucleated red cells

erythrophagocytosis were detected; in December 1958, the marrow picture was essentially similar to that of the previous aspirate; and in January 1960, minor defects were present in the cytoplasm of the late normoblasts.

Comment: The long intervals between transfusions indicated that spontaneous marrow regeneration sometimes occurred. The present remission is the longest the child has obtained, and may be related to the continuation of steroid therapy; the recent haemoglobin level of 15 g. per 100 ml. is probably higher than would be expected if the marrow were producing red cells unaided. Erythrophagocytosis was detected in the marrow examination at one stage, suggesting the possibility of an immune or haemolytic process. However, there was no collateral clinical evidence to suggest the presence of haemolysis.

Case 3. (Fig. 1) J.M., a male, was born in March 1950. His progress was normal until the age of 18 months when a severe normocytic normochromic anaemia with reticulocytopenia developed. In the first 3½ years of life only two blood transfusions were adminis-

ered, but blood transfusions were required subsequently for relief of an aregenerative anaemia on 25 occasions, at intervals of approximately three to four months. Bone marrow aspirations were performed on three occasions before the institution of steroid therapy. At the age of 2 years defective normoblastic maturation with normal erythroid proportions was noted, whilst at the age of 3 years erythroblastic hypoplasia alone was present, and at the age of 8 years erythroblastic hypoplasia was associated with defective maturation. Splenomegaly had been detected intermittently since 1954. In February 1958, prednisolone therapy was commenced in a dose of 40 mg. daily, and was accompanied by reticulocytosis and correction of the anaemia. The dose was reduced gradually and the drug was withdrawn 18 months later, at which stage mild anaemia was present. In January 1960, the haemoglobin level was 8·1 g. per 100 ml., and reticulocytopenia was evident. Marrow examination revealed erythroblastic hypoplasia (Fig. 1), defective normoblastic maturation, and a small proportion of megaloblasts. Prednisolone (20 mg. daily) was administered; marked reticulocytosis was apparent within a week, but no appreciable rise in the haemoglobin level occurred in the next fortnight, and marked macrocytosis was detected in the peripheral blood. A further bone marrow study at that stage demonstrated erythroblastic hyperplasia, the bizarre normoblasts and megaloblasts being even more prominent than on the previous occasion. Additional folic acid and vitamin B_{12} therapy were administered, and the dose of steroids was increased for two days because of vomiting. The haemoglobin level increased in three days and rose by 3·7 g. per 100 ml. over the ensuing fortnight; the reticulocyte count was usually raised, but was variable. Further marrow examinations two weeks after the commencement of combined therapy revealed improvement and a considerable reduction in the proportion of megaloblasts and abnormal erythroid elements. With reductions in the dose of prednisolone to 10 mg. daily the haemoglobin level fell, to rise again in one week when the dose was increased to 20 mg. daily. Tests performed in March 1960, revealed no evidence of achlorhydria or malabsorption, and the Schilling test was normal. The child is now receiving 15 mg. prednisolone and 20 mg. folic acid daily. He is 10 years of age and is normal in physical development.

Comment: Anaemia was not apparent until the age of 18 months, but as long remissions obtained in the first 3½ years of life, it is possible that the defect of erythropoiesis was relatively minor in infancy, and became more marked in later childhood. He subsequently received numerous transfusions before steroid therapy was commenced at the age of 8 years, when rapid haematological response ensued. Relapse occurred when steroid therapy

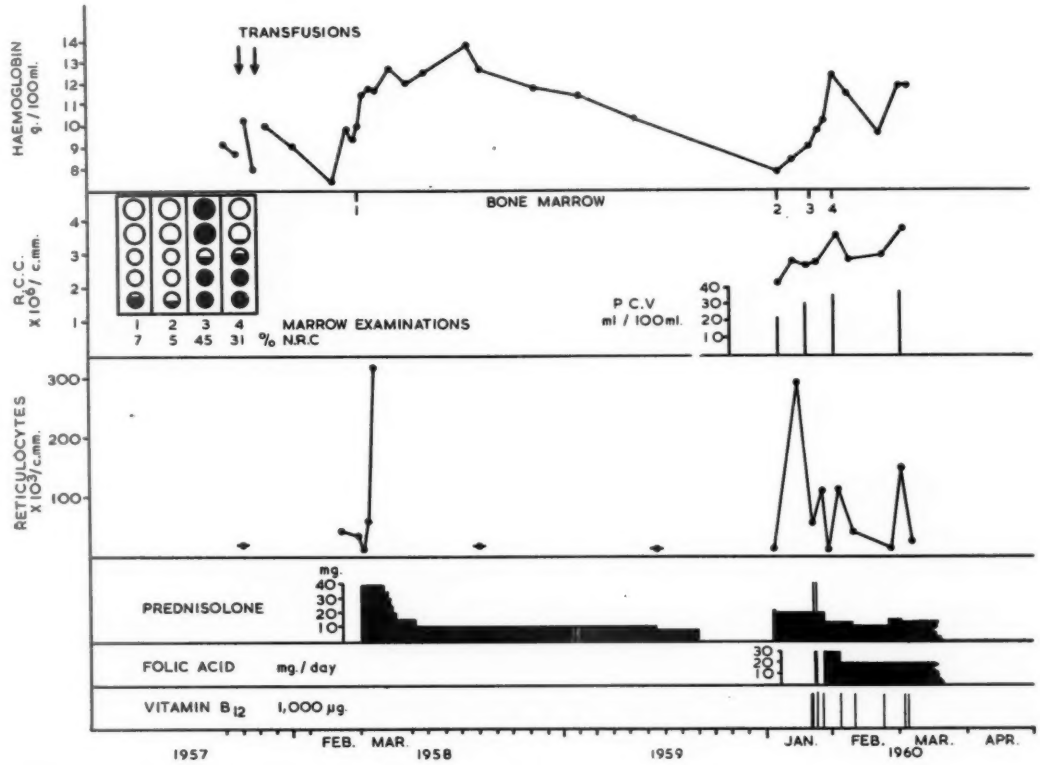

FIG. 1.—Progress of J.M. (Case 3) from the time of commencement of steroid therapy at the age of 8 years. Serial bone marrow findings (1-4) are illustrated by circles within the blocks. Each blackened circle represents 10% nucleated red cells; larger ones depict megaloblasts and smaller ones represent normoblasts.

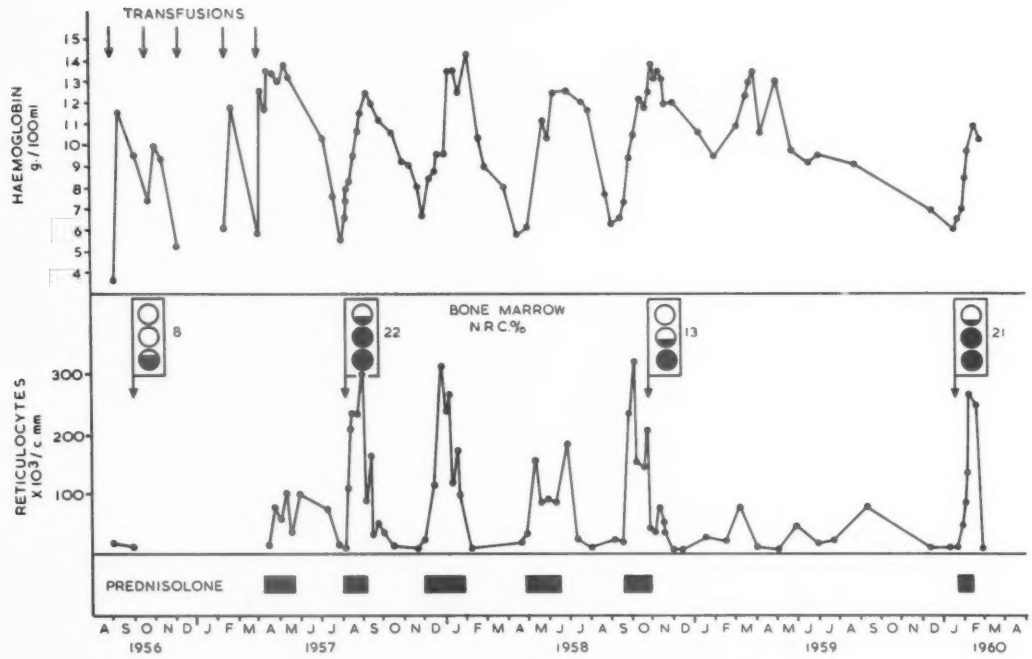

FIG. 2.—Progress of G.J. (Case 4). For legend see Fig. 1.

was withdrawn, and was associated with partial megaloblastic erythropoiesis, which became more obvious during subsequent steroid therapy. Combined vitamin B_{12}, folic acid, and steroid therapy was associated with correction of the anaemia and improvement in the marrow picture, suggesting that folic acid and vitamin B_{12} administration were partly responsible for the haematological remission.

Case 4. (Fig. 2) G.J., a male infant, was born on June 4, 1956. Increasing pallor was noted from the age of 1 month, and he was admitted to this hospital at the age of 12½ weeks with a severe orthochromic anaemia and reticulocytopenia. Blood transfusions were administered on five occasions at intervals of approximately two months, without evidence of red cell regeneration. After the last transfusion prednisolone was administered in initial doses of 25 mg. daily, and reticulocytosis and rise in haemoglobin levels appeared within a week. Steroid therapy was discontinued five weeks later. Recurrence of the anaemia with reticulocytopenia developed five times between August 1957 and January 1960, and on each occasion the administration of steroids was associated with correction of the anaemia. A satisfactory haemoglobin level was maintained without therapy for 12 months between September 1958 and September 1959. The initial marrow examination revealed erythroblastic hypoplasia, but subsequent studies during remission and relapse have shown a normal picture. The child is now 3½ years of age and is normal in mental and physical development. He has widely set eyes and prominent epicanthic folds.

Comment: On five occasions haematological remission occurred during steroid therapy, and the intervals between therapy are probably increasing. It is interesting to note that the last marrow picture during haematological relapse was entirely normal.

Case 5. (Fig. 3) S.L., a female infant of Greek parentage, was born on January 23, 1956. Exomphalos was present at birth, and required immediate surgery. At the age of 3 months the child was admitted to this hospital with a severe orthochromic anaemia; reticulocytosis was absent. Over the ensuing 21 months she received blood transfusions on 12 occasions for correction of an aregenerative anaemia. Transient pyuria was detected at the age of 8 months, and chemotherapy was administered with success. No renal abnormality was demonstrable by pyelography. The foetal haemoglobin concentration of the blood at the age of 5 months was 3·8%. In November 1957, prednisolone therapy was instituted, but it was not until 200 mg. of cortisone and later 60 mg. of prednisolone daily were administered that reticulocytosis and a rise in haemoglobin levels were detected. The dose of prednisolone was gradually reduced to 5 mg. daily over the succeeding six months, and therapy was withdrawn in October 1959. In January 1960, anaemia became apparent and the reinstitution of steroid therapy was followed by haematological remission. Bone marrow studies performed before the commencement of steroid therapy revealed normal or increased erythroid proportions and defective normoblastic maturation (Fig. 3). Subsequent examinations showed improvement, and in January 1960, the marrow appearances were normal when the child was in

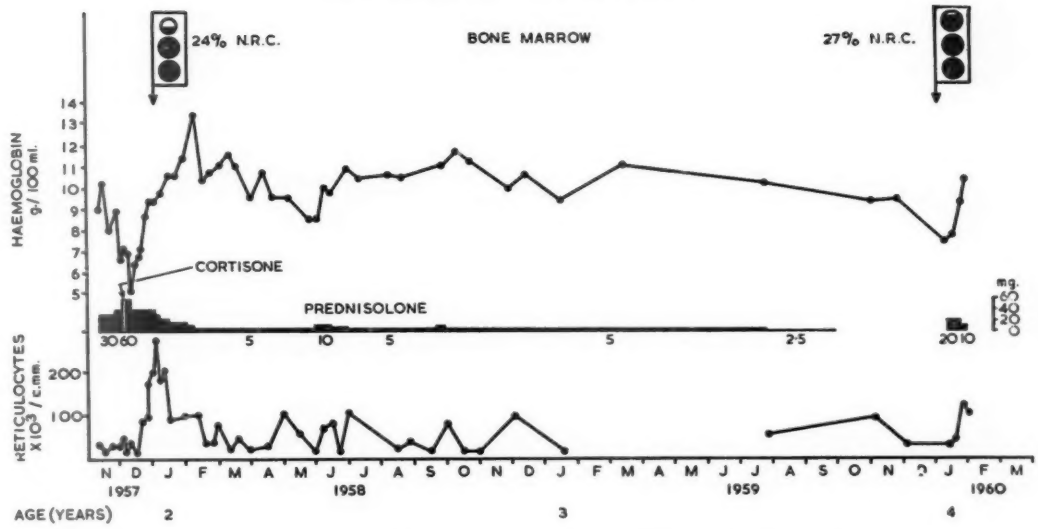

FIG. 3.—Progress of S.L. (Case 5) from time of commencement of steroid therapy.

haematological relapse. She is now 4 years old and is markedly stunted in growth and underweight. She has widely-spaced eyes, a flat nose, receding chin, webbed neck, and inverted nipples. The leucocyte chromatin pattern is positive.

Comment: The presence of exomphalos, webbed neck and dwarfism provides supportive evidence of a congenital origin of the anaemia. High doses of steroids were required to induce haematological remission, although smaller amounts were adequate for maintenance therapy. The marrow picture was normal while the child was in haematological relapse.

Case 6. (Fig. 4) K.W., a female infant, was born on August 22, 1958. Pallor was present at birth and became more marked subsequently. At the age of 7½ weeks, she was admitted to this hospital, where investigations revealed a severe anaemia, moderate macrocytosis,

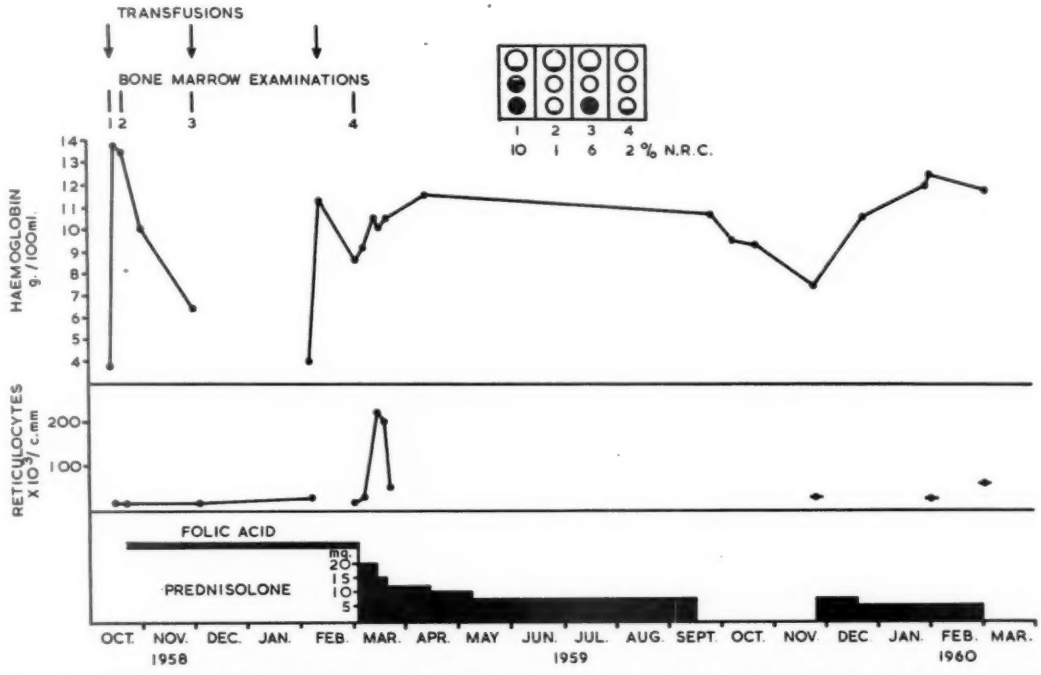

FIG. 4.—Progress of K.W. (Case 6). Each blackened circle represents 5% nucleated red cells in the marrow. Larger circles depict megaloblasts.

and reticulocytopenia. Marrow studies revealed erythroblastic hypoplasia and the presence of occasional megaloblasts. Blood transfusions were administered on three occasions at intervals of two months. Folic acid was administered for a period of six months without evidence of haematological improvement; megaloblasts did not disappear from the marrow smears for several months, but were not evident just before the commencement of steroid therapy. On March 2, 1959, folic acid therapy was withdrawn and steroid therapy was commenced. Reticulocytosis and a rise in haemoglobin level were noted nine days later, and satisfactory haemoglobin values were maintained on small doses of prednisolone, which was withdrawn in September 1959. Within two months anaemia and reticulocytopenia became apparent; prednisolone therapy was recommenced in a dose of 7·5 mg. daily and the haemoglobin value rose. At the age of 17 months, the child was of slightly less than average weight and height. She had a snub nose, widely-spaced eyes, prominent epicanthic folds and a moderately widely patent fontanelle.

Comment: Anaemia was probably present at birth and progressed slowly. Marrow examinations revealed erythroblastic hypoplasia and associated megaloblastic changes which did not disappear for many months despite a prolonged course of folic acid therapy, but were not apparent at the stage when steroid therapy was commenced. The anaemia was corrected following steroid administration and recurred when the drug was withheld.

Case 7. (Fig. 5) D.McC., a female infant, was born on May 18, 1958. Mild jaundice occurred in the first few days of life; pallor was noted at the age of 2 weeks, and became progressive. At the age of 5 months she was admitted to this hospital, where investigations revealed a severe anaemia, moderate macrocytosis and reticulocytopenia. Pyuria was detected shortly afterwards, and chemotherapy was successfully prescribed. Bone marrow examinations revealed erythroblastic hypoplasia. After the administration of blood transfusions, prednisolone was given in relatively small quantities (7·5 mg. daily). Moderate anaemia with fluctuating reticulocyte counts was present over the next few months; in January 1959, the dose of prednisolone was increased to 10 mg. daily, and the haemoglobin reached a satisfactory level after several months. The dose of prednisolone was reduced to 2·5 mg. daily in May 1959, but by October anaemia had become marked. An increase in the dose of steroids was followed by correction of the anaemia. At the age of 20 months the child was well, but was less than the tenth centile in height and weight for her age. Blue sclerae and a moderately widely patent fontanelle were noted. The spleen was just palpable. Marrow studies at that stage revealed normal proportions of red cell precursors, some of which showed imperfect haemoglobinization.

Comment: When relatively small amounts of prednisolone (7·5 to 5 mg. daily) were used initially, no impressive rise in haemoglobin values occurred. An increase in dosage was followed by correction of the anaemia over a period of several months. Relapse occurred when only 2·5 mg. of prednisolone were administered daily, and remission followed the institution of larger doses. Evidence for small stature was present before steroids were administered.

Case 8. (Fig. 6) J.A., a female infant, was born on August 29, 1959. Pallor was noted at the age of 3½ months and she received a blood transfusion in January

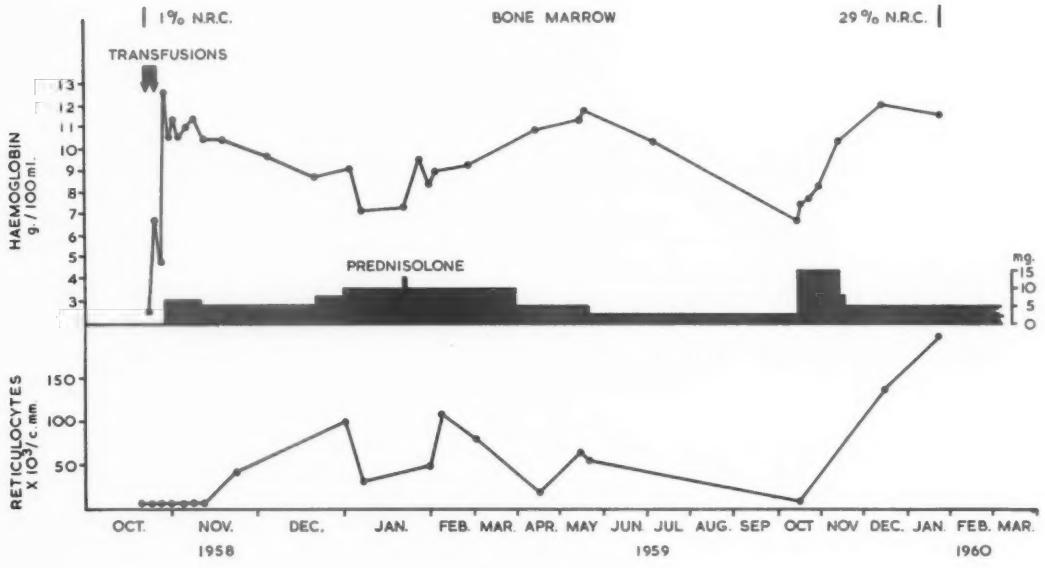

FIG. 5.—Progress of D.McC. (Case 7).

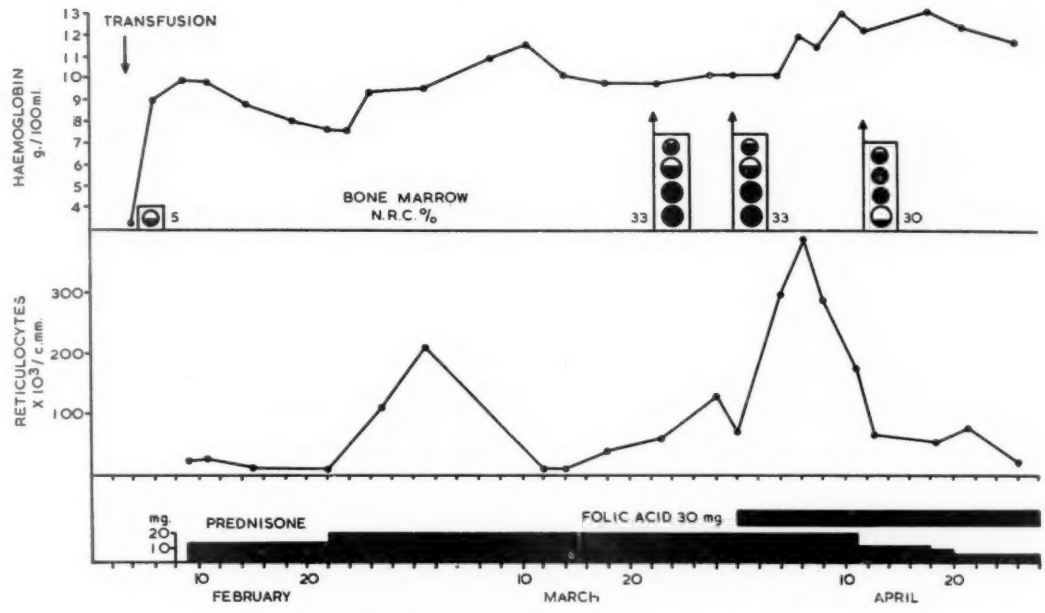

FIG. 6.—Progress of J.A. (Case 8). For legend see Fig. 1.

1960. Her feedings had consisted of a powdered milk mixture. She was transferred from the country to this hospital on February 4, at the age of 5½ months, when severe normocytic normochromic anaemia was detected. Marrow examination revealed erythroblastic hypoplasia. From the day of admission for a period of three weeks mild diarrhoea was present. After the administration of a blood transfusion on February 4, prednisone was given in a dose of 15 mg. daily without haematological response; after three weeks of therapy the dose was increased to 20 mg. daily, and within four days reticulocytosis and a rise in haemoglobin values occurred, which continued for three weeks. The haemoglobin level subsequently fell, and reticulocytopenia was noted frequently. Marrow studies on two occasions demonstrated predominantly megaloblastic erythropoiesis with defective normoblastic maturation. Folic acid (30 mg. daily) was administered in addition to prednisone; a secondary reticulocytosis and rise in haemoglobin values occurred within a few days and continued while the dose of steroids was maintained. Marrow studies after 10 days of combined therapy revealed considerable improvement. Megaloblasts were present in only small proportions, but defects in normoblastic maturation were still evident. Hepatomegaly was present during the period of observation, splenomegaly being noted only in the initial stages of hospitalization. The child was considerably dwarfed, and weighed only 10 lb. at the age of 7½ months. Physical features included short limbs, a short thick neck, and blue sclerae, her appearance resembling that of a child with achondroplasia. However, radiological examination revealed features consistent with a congenital defect of osseous development, but were not typical of any particular form of osteochondrodystrophy. Biochemical tests demonstrated no evidence of metabolic bone disease.

Comment: The presence of dwarfism and skeletal anomalies suggests that the anaemia is congenital in origin. There is no reason to suspect that the osseous abnormality is affecting red cell production. Steroid therapy was associated with temporary haematological response when the dose was increased, but regression followed, and marrow examinations revealed megaloblastic erythropoiesis. The administration of folic acid was associated with haematological remission and an improvement in the marrow picture. It is possible that the diarrhoea contributed to the folic acid deficiency.

Discussion

Clinical Features. All eight patients presented with severe anaemia at ages varying from 8 weeks to 18 months. Five were female and three were male. Most of the infants had been well previously, apart from progressive pallor, which was noted in the first month of life in three patients. Gastrointestinal symptoms were common when the anaemia became profound. Hepatosplenomegaly was present in three patients (Cases 1, 3 and 8), two of whom (Cases 1 and 3) had received numerous transfusions. Splenomegaly alone was noted at some stage of the disease in two other patients (Cases 6 and 7). The size of the spleen varied, and was not related to the haematological status of the patient. Various physical anomalies were noted in this series, of which the commonest was dwarfism (considerably less

than the tenth centile for age in height and weight) in five patients. Three of these five children had additional major anomalies, which included gross urinary tract malformations, exomphalos and a webbed neck, and a generalized skeletal abnormality. Additional features, of doubtful significance, were prominent epicanthic folds in two children, a wide fontanelle in two, blue sclerae in three, and inverted nipples in three children.

Aetiology. It was not possible to attribute the anaemia to any extrinsic factors either before or after birth. Only one mother (of Case 6) had any recognizable illness during pregnancy (hyperemesis, toxaemia, and a moderate antepartum haemorrhage) or was exposed to any unusual physico-chemical hazards (chest radiograph at six weeks' gestation; administration of chlorothiazide and reserpine in the last month of pregnancy). No history of any blood disorders in the families was obtainable. The blood groups of the mothers and patients are included in Table 1; it is extremely unlikely that isoimmunization was related to red cell depression in five of these infants (Cases 2, 4, 6, 7 and 8). The associated physical anomalies and the onset of anaemia early in life provide supportive evidence that the disturbance of erythropoiesis is congenital. Although cases have been reported (Burgert *et al.*, 1954; Kåss and Sundal, 1953; Rubell, 1942; Diamond and Blackfan, 1938) with associated neutropenia or thrombocytopenia, suggesting superficial resemblance to Fanconi's pancytopenia with multiple skeletal defects, erythroid hypoplasia appears to be a distinct entity. Steroid therapy has not proved to be an effective form of therapy in Fanconi's anaemia, whilst in erythroid hypoplasia of infancy the haematological response is often dramatic. There is a tendency to spontaneous remission in recorded cases with increasing age, and it is possible that the elaboration of sex hormones may be responsible. The benefit occasionally derived from splenectomy in childhood (Case 7 of Heaton, Crosby and Cohen, 1957), and in adult life (Loeb *et al.*, 1953) may be evidence of a further hormonal factor affecting erythropoiesis. Radiological examination of the chest failed to reveal the presence of a thymic tumour in any patient in the present series.

Peripheral Blood Picture. The most prominent haematological findings were profound anaemia and absence of reticulocytosis. In seven patients the haemoglobin value on the first admission to this hospital was less than 4 g. per 100 ml. The red cells were usually of normal morphology, although moderate macrocytosis was noted in some infants. Reticulocyte counts of 50,000 cells per c.mm. or less were present in the five patients in whom these were performed initially, and in all patients reticulocytopenia was demonstrated at subsequent examinations. Neutrophil counts were occasionally at the lower limit of normal in three children (Cases 3, 4 and 8), and thrombocyte counts were moderately reduced at some stage in three patients (Cases 1, 2 and 8). Macrocytosis and reticulocytosis were seen during steroid therapy; however, macrocytosis was not marked in one patient (Case 8) whose marrow demonstrated profound megaloblastic erythropoiesis.

Bone Marrow Studies. The bone marrow studies showed considerable variation. Before the use of steroid therapy, the following findings were noted: erythroblastic hypoplasia alone in four patients (Cases 1, 4, 7 and 8); erythroblastic hypoplasia with associated megaloblastic changes in one (Case 6); variable combinations of erythroblastic hypoplasia, normal erythroid proportions, and defective normoblastic maturation in two (Cases 2 and 3); and normal or increased erythroid proportions with defects of normoblastic maturation in one child (Case 5). Progress marrow studies were performed during steroid therapy in six patients (Cases 2, 3, 4, 5, 7 and 8). Improvement in the marrow picture was noted in four patients (maturation defect less marked in Cases 2 and 5; minor defect in Case 7; normal marrow in Case 4), but in two children (Cases 3 and 8) megaloblastic erythropoiesis and defective normoblastic maturation were detected in the early stages of steroid therapy; these abnormalities were much less prominent two weeks after the additional administration of folic acid or vitamin B_{12}. The bone marrow of three children was examined when haematological relapse occurred following the cessation of steroid administration; in two patients (Cases 4 and 5) the picture was normal, and in one child (Case 3) bizarre normoblasts and occasional megaloblasts were detected in the smears.

Despite these variable features, some pattern emerged during the study of progress marrow examinations. When erythroblastic hypoplasia was present, the morphology of the red cell precursors was usually normal; when erythroid proportions were normal or increased, defects of maturation became apparent, and were usually most marked at the late normoblast stage. The marrow picture improved after the administration of steroids, except in two instances where active erythropoiesis appeared to unmask a latent deficiency of folic

acid or vitamin B_{12}. The administration of these latter agents with steroids was associated with haematological improvement.

Other Laboratory Investigations. Blood urea levels showed transient elevation in two patients (Cases 5 and 7); the results are not available for Case 1. Pyuria was detected in three children (Cases 1, 5 and 7) and was transient in two (Cases 5 and 7); the duration of the anaemia excluded the possibilities of chronic azotaemia or infection as major aetiological factors. The direct Coombs' test was negative and the serum bilirubin level was within normal limits in all patients where these tests were performed (see Table 1). A thymic tumour was not detected in the radiological examination of the chest in any patients.

Course and Therapy. Before the advent of steroid therapy, the only consistent benefit in these patients was derived from repeated blood transfusions. Spontaneous remissions occurred in two children (Cases 2 and 3) for periods as long as 14 months. Three patients in this series received more than 25 blood tranfusions, and the remainder at least two. The only child who died (Case 1) received 82 litres of blood, and was found to have extensive haemosiderosis at autopsy.

Steroid therapy was administered to seven patients, and was associated with haematological improvement in all. In one (Case 2), intensive therapy for three weeks failed to induce haematological improvement, and a transfusion was administered. Steroid administration was continued subsequently and she has remained in haematological remission for over 14 months. As spontaneous remissions had occurred previously for periods as long as 14 months, it is possible that her present satisfactory state may be unrelated to steroid therapy. Of the other six patients, none has required transfusions since the time when steroids were first administered, representing intervals of 25, 37, 29, 13, 18 and two and a half months. There is no doubt that steroid therapy was effective, as haematological remission occurred on five occasions in one child (Case 4), and in other patients (Cases 3, 5, 6 and 7) haematological relapse developed when the drug was withdrawn or reduced in dose, to be followed by remission with the reinstitution of adequate therapy. In general, amounts equivalent to 20-30 mg. of prednisolone daily were sufficient to initiate increased red cell production, and such a response was usually evident within four to 11 days. In two patients (Cases 5 and 8) reticulocytosis and a rise in haemoglobin levels did not appear until the dose was increased, when signs of red cell regeneration became apparent in four to five days. The nature of this response suggests that the adjustment of steroid dosage may be critical, although one cannot exclude the possibility that this form of therapy may be required for several weeks to induce effective erythropoiesis.

Numerous megaloblasts were noted in marrow examinations of two children (Cases 3 and 8) during steroid therapy, and reversion to normoblastic erythropoiesis followed the additional administration of folic acid and vitamin B_{12}. In one (Case 8), megaloblastic erythropoiesis was very marked, and a well-defined haematological response followed the use of folic acid. In the other patient (Case 3), megaloblastic erythropoiesis was present to a lesser degree, and haematological improvement after the administration of vitamin B_{12}, folic acid and prednisolone was less dramatic; moreover, the daily dose of prednisolone administered during the critical period was considerably smaller than that used to induce the first remission two years earlier. The progress of J.A. (Case 8) is similar to that of the child described by Arrowsmith *et al.* (1953). When a suboptimal haematological response follows an adequate trial of steroid therapy, it seems advisable to perform further marrow examination to exclude the possibility of megaloblastic erythropoiesis; in Case 8 there was little evidence of macrocytosis in the peripheral blood picture.

Maintenance steroid therapy was usually effective when amounts equivalent to 5-10 mg. of prednisolone were administered daily, and was associated with no harmful side-effects. Relapse occurred within a few weeks or months in five patients (Cases 3, 4, 5, 6 and 7) when the drug was withdrawn or drastically reduced in dosage, so that prolonged maintenance therapy or intermittent therapy was required. It is likely that the intervals between relapse will become longer with increasing age, as suggested by the progress of Case 4. The longest period of observation of a patient with steroid administration is three years (Case 4).

It has been suggested (Gasser, 1957; Smith, 1959) that steroid therapy is of little avail when transfusion haemosiderosis has developed. Only one of the present group of patients could be considered unduly refractory to treatment (Case 2), although only two patients (Cases 2 and 3) had received many blood transfusions before steroid therapy was tried.

A variety of therapeutic regimes was adopted for patients in this series. It is suggested that blood transfusions be administered on the initial two or three occasions when anaemia develops. In doing so, it should be possible to assess the nature of the

disease and the intervals between transfusions which may be required. Moreover, haematological remissions may occur for long periods, as illustrated in Cases 2 and 3. Steroid therapy may be instituted subsequently, and it is convenient to continue maintenance treatment for a period of six to 12 months, at the end of which time the patient's requirements may be judged according to haematological progress. High doses of steroids may be required for several weeks to induce haematological remission, and the reason for therapeutic failures in other case reports may be in the administration of inadequate initial doses of steroids. Suboptimal haematological response during steroid therapy should prompt investigation into the possibility of megaloblastic erythropoiesis.

Summary

The literature concerning erythroid hypoplasia in infancy and childhood is reviewed briefly, and the details of eight further patients are presented.

All children developed a severe aregenerative anaemia at ages varying between 8 weeks and 18 months. A high incidence of associated physical anomalies was noted in this series, and included dwarfism, urinary tract malformations, exomphalos, skeletal abnormalities and webbed neck. The association of these anomalies with the onset of anaemia early in life provides supportive evidence that the aetiology of the anaemia rests in a congenital defect of the erythron.

Bone marrow studies revealed considerable variation. Erythroid elements were present in decreased, normal or increased proportions, and defects of normoblastic maturation were noted at some stage in several patients. During steroid therapy the marrow picture showed improvement in four patients, but megaloblastic erythropoiesis became prominent in two other children, and haematological improvement followed the additional administration of folic acid or vitamin B_{12}.

One patient died; the remainder are still living. Spontaneous remission for long periods occurred in two patients before the advent of steroid therapy. Steroids were administered to seven children, of whom six received definite, and one possible benefit.

High doses of steroids for several weeks may be required to induce haematological remission; suboptimal responses to adequate therapy should suggest the possibility of megaloblastic erythropoiesis.

A method of management of these patients is briefly outlined.

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References

Aldridge, A. G. V. and Kidd, P. (1953). Correspondence. *Brit. med. J.*, **1**, 729.

Altman, K. I. and Miller, G. (1953). A disturbance of tryptophan metabolism in congenital hypoplastic anaemia. *Nature* (*Lond.*), **172**, 868.

Anderson, D. E. (1952). Chronic aregenerative anaemia of the newborn. *Med. J. Aust.*, **1**, 573.

Arrowsmith, W. R., Burris, M. B. and Segaloff, A. (1953). Production of megaloblastic marrow by administration of cortisone in aplastic anemia, with subsequent response to vitamin B_{12}. A relationship not previously described. *J. Lab. clin. Med.*, **42**, 778.

Bonham Carter, R. E., Cathie, I. A. B. and Gasser, C. (1954). Aplastische Anämie (chronische Erythroblastophthise) bedingt durch Autoimmunisierung. *Schweiz. med. Wschr.*, **84**, 1114.

Bousser, J., Christol, D. Dausset, J., Rampon, S., Jallut, H. and Mery, J. P. (1955). Épisode érythroblastopénique prolongé ayant marqué le début d'une anémie hémolytique chronique avec auto-anticorps. *Sang*, **26**, 804.

Burgert, O. Jr., Kennedy, R. L. J. and Pease, G. L. (1954). Congenital hypoplastic anemia. *Pediatrics*, **13**, 218.

Calvert, R. J. and Robson, T. (1956). Cortisone therapy in erythrogenesis imperfecta. *Arch. Dis. Childh.*, **31**, 177.

Cathie, I. A. B. (1950). Erythrogenesis imperfecta. *Ibid.*, **25**, 313.

Chernoff, A. I. and Josephson, A. M. (1951). Acute erythroblastopenia in sickle-cell anemia and infectious mononucleosis. *A.M.A. Amer. J. Dis. Child.*, **82**, 310.

Dacie, J. V., Smith, M. D., White, J. C. and Mollin, D. L. (1959). Refractory normoblastic anaemia: a clinical and haematological study of seven cases. *Brit. J. Haemat.*, **5**, 56.

Diamond, L. K. (1954). Editorial comment, *Year Book of Pediatrics*, 1954-1955 series, p. 308. Year Book Publishers, Chicago.

—— and Blackfan, K. D. (1938). Hypoplastic anemia. *Amer. J. Dis. Child.*, **56**, 464.

Donnelly, M. (1953). A case of primary red cell aplasia. *Brit. med. J.*, **1**, 438.

Eisemann, G. and Dameshek, W. (1954). Splenectomy for 'pure red-cell' hypoplastic (aregenerative) anemia associated with autoimmune hemolytic disease. (Report of a case.) *New Engl. J. Med.*, **251**, 1044.

Fisher, O. D. and Allen, F. M. B. (1953). Erythrogenesis imperfecta or congenital hypoplastic anaemia (Diamond-Blackfan type). *Arch. Dis. Childh.*, **28**, 363.

Gasser, C. (1957). Aplasia of erythropoiesis. *Pediat. Clin. N. Amer.*, May, 1957, p. 445.

Harper, M. and Geikie, G. (1955). Congenital pure red cell anaemia or erythrogenesis imperfecta. *Med. J. Aust.*, **2**, 245.

Heaton, L. D., Crosby, W. H. and Cohen, A. (1957). Splenectomy in the treatment of hypoplasia of the bone marrow, with a report of twelve cases. *Ann. Surg.*, **146**, 637.

Høyer, K. (1942). Aregenerative, probably congenital, anaemia in an infant with deficiency of erythroblasts in the bone marrow. *Nord. med.*, **14**, 1097.

Josephs, H. W. (1936). Anaemia of infancy and early childhood. *Medicine* (*Baltimore*), **15**, 307.

Kåss, A. and Sundal, A. (1953). Anaemia hypoplastica congenita (anaemia typus Josephs-Diamond-Blackfan). Report of a case treated with adrenocorticotropin with effect. *Acta paediat.* (*Uppsala*), **42**, 265.

Kohlbry, C. O. (1941). Congenital hypoplastic anemia. Case report. *J. Pediat.*, **19**, 662.

Lelong, M., Joseph, R., Polonowski, C., Desmonts, G. and Colin, J. (1951). L'anémie chronique avec arrêt de la maturation normoblastique (type Blackfan-Diamond). *Arch. franç. Pédiat.*, **8**, 473.

Loeb, V., Jr., Moore, C. V. and Dubach, R. (1953). The physiologic evaluation and management of chronic bone marrow failure. *Amer. J. Med.*, **15**, 499.

Owren, P. A. (1948). Congenital hemolytic jaundice. The pathogenesis of the 'hemolytic crisis'. *Blood*, **3**, 231.

Palmen, K. and Vahlquist, B. (1950). Stationary hypoplastic anemia. *Acta haemat.* (*Basel*), **4**, 273.

Pearson, H. A. and Cone, T. E., Jr. (1957). Congenital hypoplastic anemia. *Pediatrics*, **19**, 192.

Rinvik, R. (1940). Two cases of idiopathic hypoplastic anemia in infants. *Acta paediat.* (*Uppsala*), **28**, 304.

Robson, T. and Sweeney, P. J. (1948). Chronic hypoplastic anaemia arising in infancy. *Arch. Dis. Childh.*, **23**, 294.

Rubell, I. (1942). Hypoplastic congenital anemia. *J. Pediat.*, **20**, 756.

Sup, M. (1955). Aplastic crisis in a case of immuno-hemolytic anemia. *Acta med. scand.*, **153**, 137.
Smith, C. H. (1949). Chronic congenital aregenerative anemia (pure red-cell anemia) associated with iso-immunization by the blood group factor 'A'. *Blood*, **4**, 697.
—— (1953). Hypoplastic and aplastic anemias of infancy and childhood: with a consideration of the syndrome of nonhemolytic anemia of the newborn. *J. Pediat.*, **43**, 457.
—— (1959). Pure red-cell anemia. *Ibid.*, **54**, 609.
Sundal, A. (1956). Anemia hypoplastica congenita treated with cortisone. Correction of the anemia with cortisone treatment during 4 years. *Acta paediat.* (*Uppsala*), **45**, 456.
Tsai, S. Y. and Levin, W. C. (1957). Chronic erythrocytic hypoplasia in adults. *Amer. J. Med.*, **22**, 322.
Verger and Leger (1953). Anémie hypoplastique de la première enfance (anémie de Blackfan-Diamond). *Arch. franç. Pédiat.*, **10**, 328.
Vilter, R. W., Jarrold, T., Will, J. J., Mueller, J. F., Friedman, B. I. and Hawkins, V. R. (1960). Refractory anemia with hyperplastic bone marrow. *Blood*, **15**, 1.
Wallman, I. S. (1956). Hereditary red cell aplasia. *Med. J. Aust.*, **2**, 488.

RED CELL CHOLINESTERASE IN INFANCY AND CHILDHOOD*

BY

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Little information is available on the erythrocyte cholinesterase levels in infancy and childhood. Sabine (1955) found it to be within the normal adult range for 18 children aged 3 months to 18 years, but in seven infants under 15 days of age the values varied from 57 to 75% of the mean adult value. Oka (1954) found a mean level similar to adults in 12 children aged 4 to 14. Jones and McCance (1949) estimated the red cell cholinesterase in the cord blood of 24 infants and compared it to that in 11 adults. The mean cord blood level was 61% of the adult mean. Pritchard and Weisman (1956) obtained a similar result in their 16 cases.

This paper adds further data about infants and children and shows that the immature cells in cord blood contain more cholinesterase. However, even in severe erythroblastosis foetalis the level was not above the normal range.

The method of estimating red cell cholinesterase and its range in normal adults has been described previously (Burman, 1961).

Observations

The red cell cholinesterase was determined on blood from 58 children aged 2 to 19 years seen at the Hospital School. All these children had a mean corpuscular haemoglobin concentration above 30%, and most of them suffered from a chronic neurological disorder for which they were having in-patient care. The mean and standard deviation of the 58 cases was 9·57 ± 1·06 units per ml. red blood cells with a standardized range (mean ± 2 S.D.) of 7·45 to 11·69 units. There was no significant difference between the sexes and no correlation with age (Fig. 1). The negative correlation with haemoglobin content ($r = -0{\cdot}3010$) was significant at the 5% level and with the mean corpuscular haemoglobin concentration ($r = -0{\cdot}3614$) at the 1% level.

Twenty infants under the age of 2 were studied. These infants were in-patients of the nursery of the Paediatric Department of the University Hospitals, Iowa City, and suffered from a variety of diseases. Many of them were anaemic with a low mean corpuscular haemoglobin concentration. The age distribution of these infants is shown in Fig. 2. No case aged 5 months or more had an activity below the normal adult range and no case aged 2 months or less had an activity higher than normal cord blood.

Samples of cord blood were collected from 57 normal babies born in the Obstetric Unit of the University Hospitals between January and April 1959. These infants were all singletons delivered *per vaginam* and all had a negative direct Coombs' test. No abnormality was detected during their stay of about five days in the newborn nursery. Of the 57 specimens, 27 had clotted. No difference was found between the mean red cell cholinesterase content of the clotted and successfully heparinized specimens ($t = 0{\cdot}551$). The mean cholinesterase activity of the 57 cases was 5·29 units per ml. red cells with a standard deviation of 1·09 units and a standardized range of 3·11 to 7·47 units. The distribution of these 57 observations is shown as

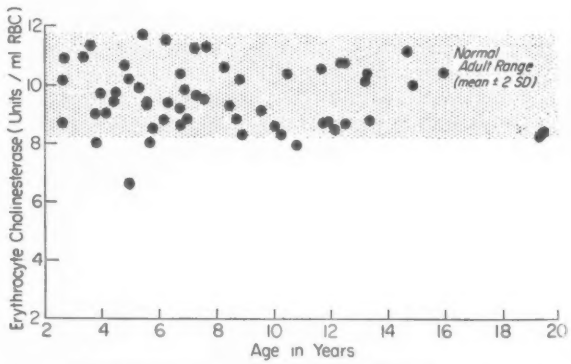

FIG. 1.—Red cell cholinesterase activity in 58 children aged 2 to 19 years without haematological disease.

* This work formed part of an M.D. Thesis for the University of London.

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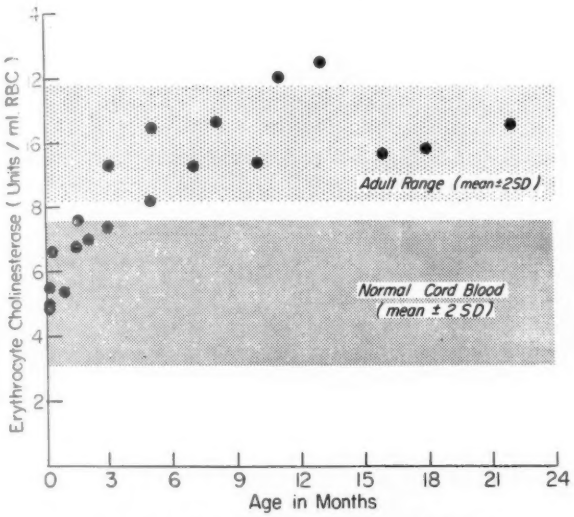

FIG. 2.—Red cell cholinesterase activity in 20 sick infants.

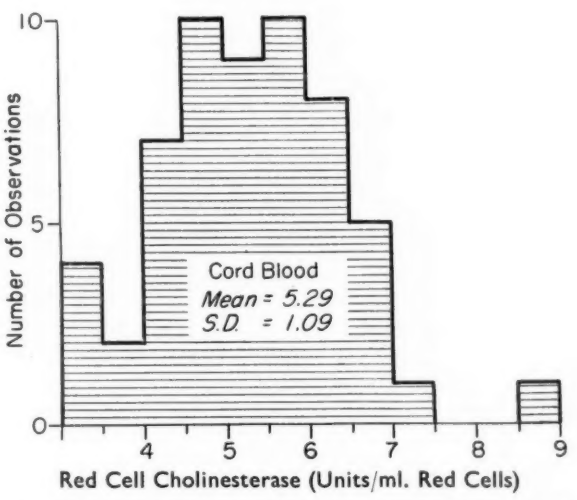

FIG. 3.—The distribution of the red cell cholinesterase activity in cord blood from 57 normal infants.

a histogram in Fig 3 and is 'normal'. There is no difference between the sexes and no correlation with birth weight, haemoglobin concentration, packed cell volume, reticulocyte count and normoblasts per c.mm. The negative correlation with the mean corpuscular haemoglobin concentration ($r = -0{\cdot}3949$) was significant at the 5% but not the 2% level.

Partial haemolysis of cord red cells was performed by adding 1 ml. washed red cells (packed cell volume = about 0·50) to 5 ml. 0·36 or 0·32% saline. The mixture was inverted five times and allowed to stand for 10 minutes. The cells resistant to haemolysis were then washed twice with physiological saline and their cholinesterase content determined. The degree of haemolysis was estimated by comparing the haemoglobin concentration of the supernatant with that of a similar tube in which complete haemolysis had been produced by distilled water. In view of the changes in red cell volume which occur when red cells are exposed to hypotonic saline, the cholinesterase is measured in terms of haemoglobin. The results of six experiments are shown in Table 1. The cholinesterase after haemolysis was higher in every case. The mean difference of the six observations before and after haemolysis was 6·32 units. This can be compared with the experimental error of the estimation by a 't' test. The standard deviation of the difference of two estimations due to experimental error was calculated by multiplying the standard deviation of duplicate estimations (0·72 units per gram haemoglobin) by the square root of 2. The value of 't' was 6·2083. With 5 degrees of freedom, this is significant at the 1% level. The correlation between the percentage of haemolysis and the increase in red cell cholinesterase ($r = +0{\cdot}8134$) is significant at the 5% level.

The red cells were separated by centrifuging the heparinized blood at 3,000 r.p.m. (1,500 g.) for 10 minutes. The top and bottom layers were then separated and each layer washed three times in physiological saline. The cholinesterase was estimated on both samples and a specimen of washed red cells which had not been centrifuged. The cholinesterase was measured in terms of haemoglobin because centrifuging separates cells of different densities and different volumes. The results of five experiments are shown in Table 2. The cholinesterase of the cells in the upper layer was higher than that before centrifuging in every case. The mean difference was 3·20 units and this differed significantly from the experimental error ($t = 3{\cdot}1434$; $df = 4$; $p < 0{\cdot}05$). The mean cholinesterase of

TABLE 1

EFFECT OF PARTIAL HAEMOLYSIS OF ERYTHROCYTES FROM CORD BLOOD UPON CHOLINESTERASE CONTENT OF CELLS WHICH ARE NOT HAEMOLYSED

Case No.	Strength of Saline	Degree of Haemolysis (%)	Cholinesterase (units per g. Hb)		
			Before Haemolysis	After Haemolysis	Difference
1	0·36	46	17·3	24·2	6·9
2	0·36	54	21·3	25·7	4·4
3	0·36	21	16·9	20·9	4·0
4	0·32	73	22·7	31·4	8·7
5	0·36	49	21·0	26·8	5·8
6	0·32	67	21·0	29·1	8·1

TABLE 2
CHOLINESTERASE CONTENT OF RED CELLS OF CORD BLOOD AFTER CENTRIFUGAL SEGREGATION

Case No.	Fraction	Red Cell Cholinesterase (units per g. Hb)	Difference
1	Upper	17·2	+ 2·5
	Unseparated	14·7	
	Lower	13·5	− 1·2
2	Upper	23·9	+ 4·2
	Unseparated	19·7	
	Lower	20·0	+ 0·3
3*	Upper	21·3	+ 3·7
	Unseparated	17·6	
	Lower	13·4	− 4·2
4	Upper	19·7	+ 1·5
	Unseparated	18·2	
	Lower	17·7	− 0·5
5	Upper	23·8	+ 4·1
	Unseparated	19·7	
	Lower	19·8	+ 0·1

* Case of erythroblastosis foetalis.

the lower layer was 0·90 units less than the mean of the unsegregated samples; this difference was not significant ($t = 0·8841$). In two cases the lower layer had more cholinesterase than the original specimen, but these differences were within experimental error.

The cord blood from 11 cases of erythroblastosis foetalis was studied. Nine of these cases were due to Rh incompatibility and two to ABO incompatibility. In all the Rh cases, the mother's serum contained antibodies and the direct Coombs' test was positive in cord blood. All the cases had at least one exchange transfusion except one case which required no treatment. ABO haemolytic disease was diagnosed if the mother was group O and the infant A or B, if the mother's serum contained a haemolysin against adult A or B cells, and if the infant showed signs of excessive haemopoiesis and developed jaundice within 24 hours of birth. The results of the 11 cases are shown in Table 3. All the values of erythrocyte cholinesterase were within the normal range. Of the nine cases due to Rh incompatibility only two were below the normal mean and one of these was the mildly affected infant who required no treatment. The mean cholinesterase content of the nine cases of haemolytic disease was 5·56 units per ml. red cells, but this is not significantly higher than the mean for normal cord blood.

TABLE 3
RED CELL CHOLINESTERASE IN NINE CASES OF ERYTHROBLASTOSIS DUE TO RH AND TWO TO ABO INCOMPATIBILITY

Case No.	Haemoglobin Concentration (g./100 ml.)	Reticulocytes (%)	Units of Red Cell Cholinesterase
Rh Incompatability:			
1	12·5	12·1	6·6
2	8·4	32·5	5·3
3	6·0	53·3	4·8
4	10·0	3·7	6·0
5	14·1	5·1	6·4
6	Specimen clotted but infant severely affected	—	5·6
7*	15·0	3·8	3·8
8	Specimen clotted but infant severely affected	—	6·0
9	15·5	5·1	5·5
ABO Incompatibility:			
10	16·5	4·9	3·2
11	11·6	12·7	5·0

* Required no treatment.

Discussion

With the same method of estimating red cell cholinesterase, the mean and standard deviation in 71 haematologically normal adults is $9·96 \pm 0·90$ units (Burman, 1961). These figures do not differ significantly from those found for the 58 children reported here. The two series can therefore be combined and the mean of the 129 observations is 9·78 units with a standard deviation of 0·97. The red cell cholinesterase in cord blood is lower than in adults and only one case lies within the adult range. The mean cord blood level is 53% of the adult mean. This figure is in general agreement with, although a little lower than that found by Jones and McCance (1949), Sabine (1955) and Pritchard and Weisman (1956). The data in infancy recorded here are not reliable as many of the infants studied were both ill and anaemic, but the adult blood level appears to be reached between 3 and 5 months of age and this agrees with the scanty data of Sabine (1955). It is at about this age that the red cell population changes from foetal cells to those produced after birth, so it is probable that the low cholinesterase content of cord cells reflects a difference between foetal and post-natal red cells.

Cells which are relatively resistant to haemolysis have been shown to be young cells (Marks and Johnson, 1958). If whole blood is centrifuged, the top layer contains the younger cells (Borun, Figueroa and Perry, 1957). Both these manoeuvres with cord blood show that young cells contain more cholinesterase than mature cells and with partial haemolysis the rise in cholinesterase is proportional to the degree of haemolysis. Similar results have been found in human adults by Allison and Burn (1955) and in adult rats by Pritchard (1949). Many clinical observations also suggest that young cells

contain increased quantities of cholinesterase for a high level is often found when there is a reticulocytosis (Meyer, Sawitsky, Ritz and Fitch, 1948; Sabine, 1951; Scudamore, Vorhaus and Kark, 1951; Sabine, 1959). In these circumstances, the red cell cholinesterase should be increased in erythroblastosis foetalis, but this was not observed in the 11 cases studied, although several were severely affected with high reticulocyte counts.

Summary

The mean cord blood red cell cholinesterase is only 53% of the adult mean. The adult level is reached between 3 and 5 months of age. Young cord red cells contain more cholinesterase than older cells. In 11 cases of erythroblastosis foetalis the red cell cholinesterase was within the normal cord blood range.

I am grateful to Dr. R. R. Rembolt for continual help and encouragement during this investigation.

References

Allison, A. C. and Burn, G. P. (1955). Enzyme activity as a function of age in the human erythrocyte. *Brit. J. Haemat.*, **1**, 291.

Borun, E. R., Figueroa, W. G. and Perry, S. M. (1957). The distribution of Fe^{59} tagged human erythrocytes in centrifuged specimens as a function of cell age. *J. clin. Invest.*, **36**, 676.

Burman, D. (1961). An electrometric method for the estimation of red cell cholinesterase. In the press.

Jones, P. E. H. and McCance, R. A. (1949). Enzyme activities in the blood of infants and adults. *Biochem. J.*, **45**, 464.

Marks, P. A. and Johnson, A. B. (1958). Relationship between the age of human erythrocytes and their osmotic resistance: a basis for separating young and old erythrocytes. *J. clin. Invest.*, **37**, 1542.

Meyer, L. M., Sawitsky, A., Ritz, N. D. and Fitch, H. M. (1948). A study of cholinesterase activity of the blood of patients with pernicious anemia. *J. Lab. clin. Med.*, **33**, 189.

Oka, M. (1954). Studies on the cholinesterase activity of red cell, plasma and synovial fluid with special reference to rheumatic diseases. *Acta med. scand.*, Supplement 293.

Pritchard, J. A. (1949). Erythrocyte age and cholinesterase activity. *Amer. J. Physiol.*, **158**, 72.

—— and Weisman, R., Jr. (1956). Erythrocyte cholinesterase activity in normal pregnancy and in megaloblastic and other anemias of pregnancy and the puerperium. *J. Lab. clin. Med.*, **47**, 98.

Sabine, J. C. (1951). The cholinesterase of erythrocytes in anemias. *Blood*, **6**, 151.

—— (1955). The clinical significance of erythrocyte cholinesterase titers. 1. A method suitable for routine clinical use, and the distribution of normal values. *Ibid.*, **10**, 1132.

—— (1959). Erythrocyte cholinesterase titers in hematologic disease states. *Amer. J. Med.*, **27**, 81.

Scudamore, H. H., Vorhaus, L. J., II and Kark, R. M. (1951). Observations on erythrocyte and plasma cholinesterase activity in dyscrasias of the blood. *Blood*, **6**, 1260.

PRIMARY MYOCARDIAL DISEASE IN INFANCY: CLINICAL ASPECTS

BY

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(RECEIVED FOR PUBLICATION NOVEMBER 7, 1960)

Primary myocardial disease is a clinical group of disorders with some features in common. Included in it are disorders in which the heart is mainly affected, with cardiomegaly and with suggestive or characteristic electrocardiographic changes; excluded from it are congenital cardiac malformations and known systemic disorders with only slight cardiac involvement. The inclusion of cases is rather arbitrary: thus, anomalous L. coronary artery is included, even though it is a congenital malformation, and glycogen storage disease of the heart, calcification of the coronary arteries and possibly virus myocarditis are included, even though extracardiac lesions occur and sometimes predominate. It is clear that the boundaries of the group will change, as more is learned of aetiology and pathology, but from the clinician's viewpoint the grouping is convenient and useful.

In a considerable proportion of published cases the diagnosis has been established only at autopsy. For this reason, and because primary myocardial disease is commonest in infancy, a broad clinical description of the group is presented, based on data from 27 infants (Table 1). Differential diagnosis of disorders within the group is discussed, particularly in relation to effective treatment.

The Present Series

All the patients were under 1 year of age when first seen. Thirteen were examined personally; records, investigations and autopsy specimens of the remainder were contributed by colleagues.

TABLE 1

27 INFANTS WITH PRIMARY MYOCARDIAL DISEASE

Myocardial Disease	Nos.
Glycogen storage disease of heart	1
Coronary artery calcification	1
Aberrant left coronary artery	4
Myocarditis	6
Endocardial fibroelastosis	15

Twenty-one of the 27 died, and in all these autopsy was carried out.

In the infant with *glycogen storage disease* of the heart the clinical diagnosis was made, and confirmed by muscle biopsy, at 3 months of age. Death occurred at 6 months. *Calcification of the coronary arteries* was found microscopically at autopsy in an infant, 3 months old, who died within a few hours of admission to hospital with acute bronchopneumonia. The mother's blood gave positive reactions to tests for toxoplasmosis. The diagnosis of *aberrant left coronary artery* was made in three of four cases during life; one of the patients survives, at the age of 2 years. Five of six infants with *myocarditis* died; the surviving one is alive and well at 2 years of age. Two presented with paroxysmal tachycardia; in one the diagnosis of primary myocardial disease (possibly endocardial fibroelastosis) had been made clinically; the remaining three died with acute heart failure before investigations could be carried out. Of the cases diagnosed as *endocardial fibroelastosis*, nine had been diagnosed in life; four of these survive and are now 2, 2, 3 and 8 years old respectively.

Clinical Picture

Family History. A family history of a similar disorder is sometimes obtained in children with glycogen storage disease of the heart or with endocardial fibroelastosis. In the present series two infants with endocardial fibroelastosis were cousins; the sibling of another probably died of the same disorder.

History. In most cases the description obtained was of a persistent or episodic disorder, usually of a few months' duration, beginning at 2 or 3 months of age or even, in a few, during the first weeks or days of life. There was a history of laboured breathing, wheeziness, 'chestiness' or lung 'infections', sometimes with slight cyanotic episodes.

Failure to thrive was common. A few infants had suffered from unexplained bouts of vomiting.

In about one-third of the cases there was no relevant previous history, and the first attack was acute and fulminating.

Examination. Three-quarters of all the cases were in heart failure when first examined. In these tachycardia and tachypnoea were observed, and in nearly all moist sounds were audible in the lungs and the liver was enlarged. Oedema and distension of the neck veins were uncommon. Slight, or occasionally marked, cyanosis was observed in half the infants with heart failure.

In all cases the heart was enlarged, whether in failure or not. The most useful method of detecting cardiac enlargement clinically was by palpation with a finger inserted under the xiphoid process.

In one-quarter of the cases a soft, systolic murmur was audible, usually along the left sternal border.

Investigations. In most cases radiograph of the chest was taken, and confirmed or revealed the cardiac enlargement. On radioscopy the left ventricle was sometimes seen to be predominantly enlarged, and cardiac pulsations were usually diminished.

As a rule E.C.G. showed a left ventricular strain pattern (see below). Other investigations were carried out in some cases and included the following: Examination of the blood to exclude severe anaemia and leukaemia; blood culture when septicaemia was suspected; serological studies for coxsackie virus and toxoplasmosis; examination of the urine to exclude renal disease and medial arterial necrosis; serum transaminase estimations (in two cases of anomalous L. coronary artery, and two of endocardial fibroelastosis). In the cases included in this series such of these tests as were done were negative (unfortunately, toxoplasma investigations were not carried out in the infant with calcified coronary arteries, in whom they might have proved positive).

Diagnosis and Differential Diagnosis

The first stage in diagnosis is usually the detection of cardiac enlargement and, as a rule, suggestive E.C.G. changes in an infant with no significant cardiac murmur and little or no cyanosis (except possibly in a phase of severe heart failure).

The next stage is the exclusion of congenital malformations of the heart and great vessels, and of systemic disorders not principally affecting the heart. Table 2 groups conditions that may simulate primary myocardial disease, in older children as well as in infants. Exclusion can be attempted only as far as is practicable clinically, and is rarely complete even at autopsy.

TABLE 2
CONDITIONS EXCLUDED AT ALL AGES

I. Cardiac Disorders:

Congenital malformations of heart and great vessels
Functional arrhythmias without demonstrable organic basis
Tumours, e.g. rhabdomyoma, sarcoma, myxoma

II. Systemic Disorders:

Infectious
(*a*) Bacterial, e.g. diphtheria, typhoid, pneumonia, septicaemia, bacterial endocarditis
(*b*) Virus, e.g. poliomyelitis, influenza, measles, varicella, mumps, glandular fever
(*c*) Parasitic and fungus, e.g. toxoplasmosis, histoplasmosis, trichiniasis, coccidiomycosis

Mesenchymal
Rheumatic carditis, rheumatoid disease, disseminated lupus erythematosus and related diseases

Endocrine and Metabolic
Hyperthyroidism, cretinism, Cushing's disease, progeria, gargoylism, beri-beri

Haematological
Leukaemia, haemolytic anaemias, abnormal haemoglobins severe iron deficiency

Neuromuscular
Friedreich's ataxia, progressive muscular dystrophy

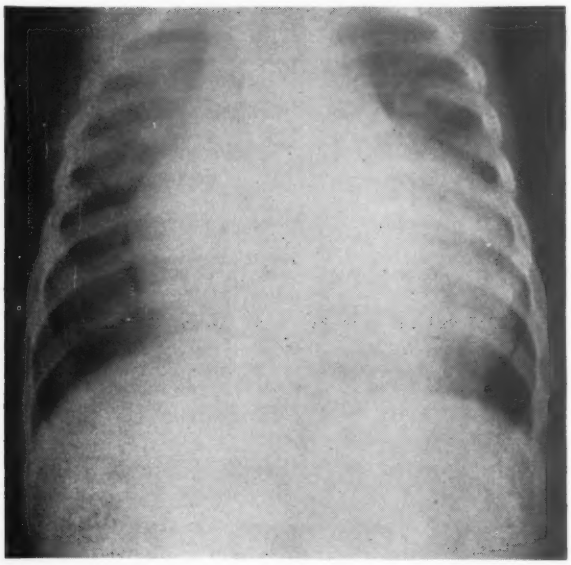
Miscellaneous
Renal disease, hypertension (essential, endocrine, encephalitic, lead poisoning), arachnodactyly, carcinoid of intestine

When the presumptive diagnosis of primary myocardial disease has been made, the next step is differential diagnosis within the group. At the present time six entities are usually included. Table 3 summarizes the main distinguishing features

TABLE 3
PRIMARY MYOCARDIAL DISEASE: DIFFERENTIAL DIAGNOSIS

Disorder	Diagnostic Features
Group A:	
Glycogen storage disease of heart	Muscles flabby; large tongue usual; E.C.G.: exaggerated LV strain pattern; muscle biopsy shows excess glycogen
Aberrant L. coronary artery	'Anginal' attacks with feeding or crying;* radioscopy may show aneurismal L. ventricle; E.C.G.: deep Q in leads I and V_5
Calcification of coronary arteries	Arterial calcification may be seen on radiograph
Medial necrosis of coronary arteries	Other congenital anomalies common; microscopic haematuria and other urinary abnormalities
Group B:	
Myocarditis	Congestive failure common; E.C.G. may show arrhythmias and low voltage
Endocardial fibroelastosis	Congestive failure common; E.C.G.: L. ventricular strain pattern usual

* Similar attacks have been observed occasionally in coarctation of the aorta and in endocardial fibroelastosis.



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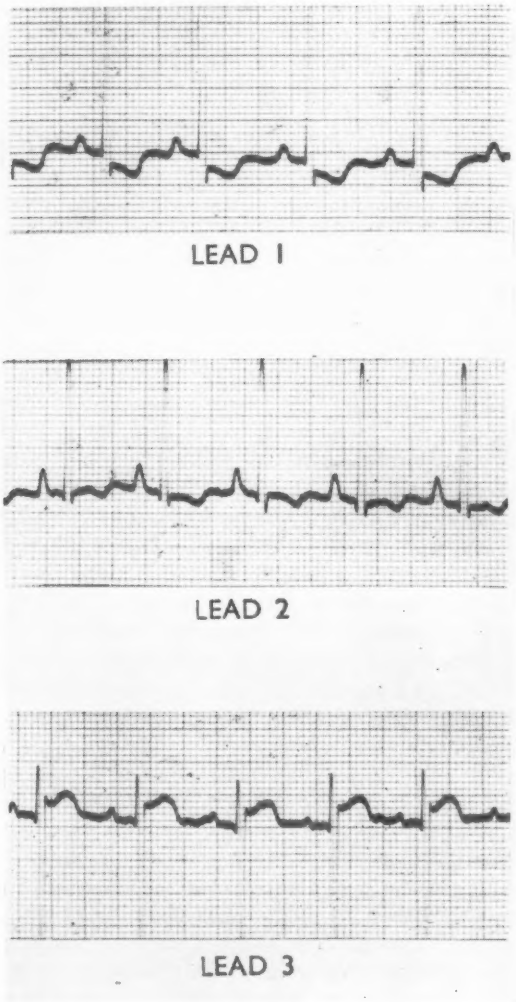

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FIG. 1.—Endocardial fibroelastosis.

(*a*) Chest radiograph at 4 months of age. (*b*) E.C.G. standard leads. (The patient is alive and well at 2 years of age.)

in the clinical differential diagnosis; it also foreshadows a sub-division according to the likely response to treatment (see further).

Electrocardiographic Abnormalities. The E.C.G. changes warrant discussion because of their importance in diagnosis. It should be emphasized, however, that diagnosis cannot be made without clinical and other examinations, for E.C.G. changes similar to those of primary myocardial disease may occur in other disorders (see Table 2).

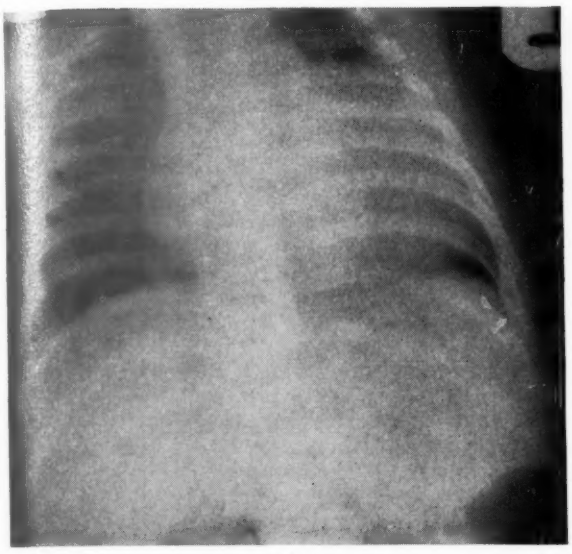
Endocardial Fibroelastosis. Primary endocardial fibroelastosis (not occurring in association with congenital malformations) illustrates the basic E.C.G. pattern of the group. This is an infantile left ventricular strain pattern (Fig. 1), usually most evident in the left precordial leads, though there is a considerable range of variations.

Characteristically, the S-T level is depressed or elevated. The T wave tends to be small, isoelectric or inverted, especially in leads I, V_5 and V_6 with a horizontal heart or in leads II, III, V_5 and V_6 with a vertical heart. In addition, there is usually a tall upright QRS, indicative of ventricular hypertrophy, and often exaggeration of P waves which suggests auricular enlargement.

The diagnosis of endocardial fibroelastosis is made by exclusion, if the basic E.C.G. pattern occurs with cardiomegaly and there are no specific features to indicate other disorders. In some cases of isolated myocarditis, however, the E.C.G. pattern may be indistinguishable from that of endocardial fibroelastosis; the two disorders may occur together (as in one fatal case in the present series). It is important to bear in mind also that with endocardial fibroelastosis, particularly the acute, fulminating cases, the E.C.G. pattern may be atypical; while in more chronic cases the typical pattern may take time to develop. Thus, in one case in the present series minimal E.C.G. changes, originally of doubtful significance, became characteristic of fibroelastosis three months later.

In infants having digitalis the E.C.G. pattern of fibroelastosis may be mimicked in the absence of this disorder, or distorted if it is present.

In *glycogen storage disease of the heart*, the E.C.G.



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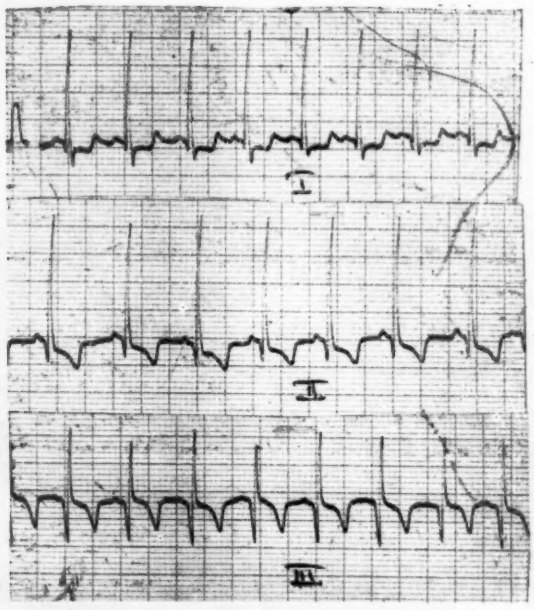

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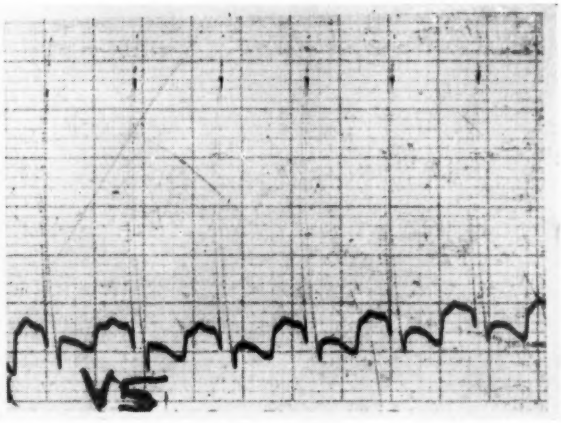

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FIG. 2.—Glycogen storage disease of heart.

(*a*) Chest radiograph at 3 months of age. (*b*) E.C.G. standard leads. (*c*) E.C.G. lead V_5.

changes may be so grossly exaggerated as to be diagnostic. A typical example is shown in Fig. 2 (in which the voltages were reduced by one-third to permit recording), which bears a remarkably close similarity to the E.C.G.s of the few published cases.

In most cases of *aberrant left coronary artery* the E.C.G. pattern is characteristic (Keith, 1959) and is similar to that of anterior myocardial infarction in the adult. A typical tracing (Fig. 3) shows a deep Q wave, most marked in leads I and V_5, together with S-T elevation and T wave inversion. In lead III S-T is depressed and T upright.

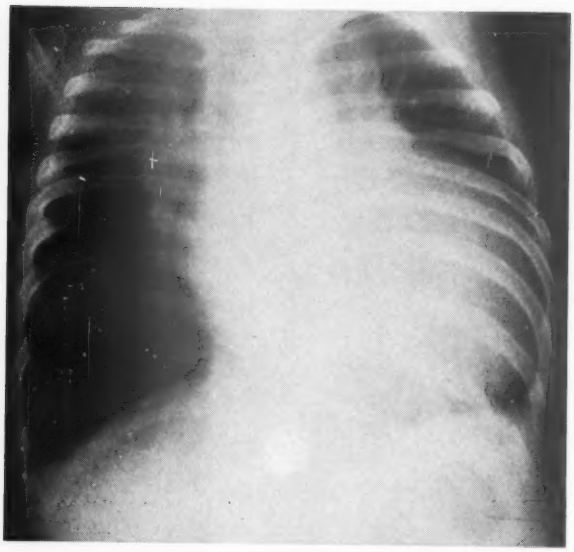
In *myocarditis* the left ventricular strain pattern may also be seen, though the changes are inconstant and often minimal. Voltages may be low and variable and T waves flattened. Prolongation of the P-R interval, or some other conduction disturbance, is much commoner than in other forms of primary myocardial disease. In some cases arrhythmia is the predominant feature, clinically and electrocardiographically. Thus, two cases in the present series were originally diagnosed as paroxysmal supra-ventricular tachycardia; in the fatal case the region of the sino-auricular node was the site of a haemorrhage (Apley, Corner and Gibson, 1955).

In *medial necrosis* and in *calcification of coronary arteries* the E.C.G. changes may be those of left ventricular strain, but are not specific (Rosenbaum, Nadas and Neuhauser, 1953), and differential diagnosis depends on other investigations.

Prognosis

From the point of view of prognosis, the primary myocardial disorders may be divided into two groups (Table 3).

Group A. The individual anomalies in this group are rare, but may be diagnosable in life (Table 3), unless investigations cannot be carried out because of the rapid course of the illness. In this group there is at present no effective treatment. Occasionally, however, an infant with aberrant L.



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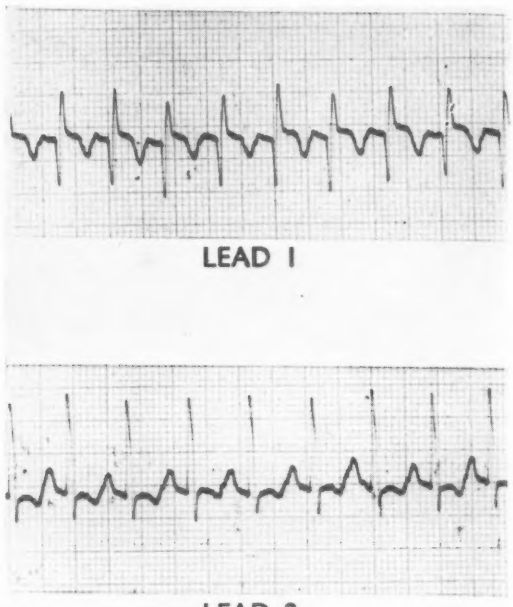

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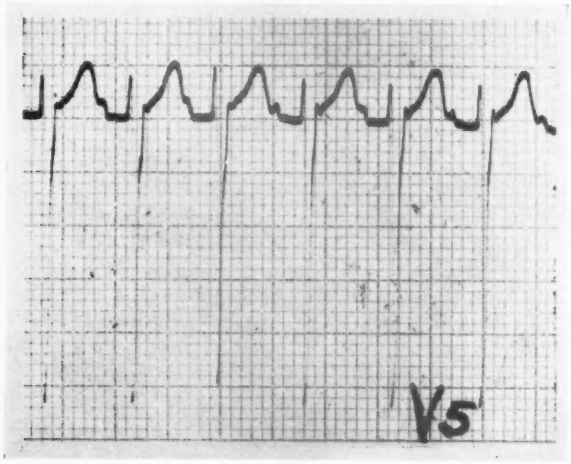
FIG. 3.—Anomalous left coronary artery.
(*a*) Chest radiograph at 2 months of age. (*b*) E.C.G. standard leads. (*c*) E.C.G. lead V_5.



(*c*)

coronary artery does survive into adult life.* Two of the cases in the present series were operated on, and various operations to correct the anomaly have been suggested (Apley, Horton and Wilson, 1957), but so far without success.

Group B. In the second and commoner group the prognosis is much better, but depends to a large extent on treatment. In this group, as compared with the first, congestive cardiac failure is a prominent feature. It seems possible that it is the effective treatment of the congestive failure that permits eventual recovery from the underlying disease.

When endocardial fibroelastosis is diagnosed, and the child recovers, doubts as to the diagnosis may be entertained. If a heart with severe, isolated endocardial fibroelastosis is examined after death it is difficult to believe that recovery in severe cases could ever be possible; yet infants with clinical and other findings indistinguishable from those of the fatal cases can and do recover. It could be assumed that the milder cases alone recover, but there is no conclusive evidence to support this. Alternatively, it may be that those who recover were, in fact, suffering not from endocardial fibroelastosis,

* It has been stated that early death is inevitable if symptoms occur in infancy (Keith, 1959), but I have recently seen a girl aged 12 (a patient of Dr. F. W. Brimblecombe), with the criteria of anomalous L. coronary artery, who was markedly breathless in infancy.

but from myocarditis or from some other clinically indistinguishable disorder. These doubts cannot at present be resolved; but since digitalis therapy may prove effective in this group of disorders it should be prescribed, even if the diagnosis of endocardial fibroelastosis is accepted with reservations.

Writing of endocardial fibroelastosis, Keith and his co-authors (Keith, Rowe and Vlad, 1958), state: 'The prognosis more or less depends on recognition and digitalis therapy.' Most of Keith's cases survived, while his untreated or inadequately treated cases died. In Nadas's (1957) series nearly half survived, almost all with digitalis therapy. In the present series four cases diagnosed as endocardial fibroelastosis and one diagnosed as myocarditis survived; but a high proportion of the cases that succumbed were seen for the first time only when moribund. In two fatal cases recovery might have been possible: in one digitalis was discontinued soon after heart failure had been corrected, and in the other it was discontinued in error after three months.

The prognosis depends not only on early, adequate and prolonged digitalis therapy, but also on other factors. Thus, the fulminating case may die within a few hours of the onset of symptoms, despite treatment; the mortality rate varies with the proportion of fulminating cases seen, and in the present series this was higher than the 25% described by Dennis, Hansen and Corpening (1953). A relapse after an initially good response to treatment is ominous. It is generally agreed that the mortality rate is higher if symptoms and signs of the illness occur in the first weeks or months of life, as compared with the end of the first year or later.

In those infants in Group B who survive recovery is apparently complete. Cardiac function seems to be unaffected, the size of the heart gradually returns to normal, and the abnormalities in the E.C.G. disappear. The return to normal according to the present series, however, takes place over a period of years rather than months.

Treatment

Under this heading the disorders in Group B alone are considered here. Diagnosis should, if possible, be established before the patient is *in extremis*, to give treatment its best chance. The essential of treatment is digitalization, and oxygen and antibiotics are usually given in addition. The infant's distress may be alleviated if the head and shoulders are propped up and maintained in this position. Morphine, diuretics, a low salt diet and steroids have also been given in some cases, but it is difficult to decide how much they help.

In the treated cases in the present series digoxin was used. The oral digitalizing dose for infants is between 0·04 and 0·06 mg. per lb. body weight; half the dose is given at once and the remainder in divided doses over the first 24 hours. If the patient is gravely ill an initial dose may be given parenterally, and should be half the calculated oral dose. The daily maintenance dose, given orally, is about one-quarter of the digitalizing dose. These figures are only guides: in children, as in adults, digitalization is an individual matter and the optimal dose for each patient can be determined only by careful observation. The digitalizing dose may be repeated if a good response has not occurred and there is no evidence of toxicity. In infants the only common clinical evidence of overdosage is vomiting, though coupled beats occasionally occur. A satisfactory response is judged not on E.C.G. changes but clinically, by slowing of the pulse, occasionally by disappearance of a gallop rhythm, and by improvement in the infant's general condition. The patient looks better, the respiration rate and raised temperature fall, the size of the liver decreases, and moist sounds in the lungs disappear.

In endocardial fibroelastosis there may be a critical level for the dosage of digitalis. A little above the optimal level for the individual, vomiting may occur; a little below it, signs of cardiac failure persist. Since the weight of an infant increases so rapidly, the amount of digitalis may need to be increased proportionately in long-continued treatment. If the infant acquires an infection, or if heart failure recurs, the dose of digitalis should be increased promptly.

Experience suggests that it is advisable to continue giving digitalis long after the acute illness has subsided. It seems a wise precaution to continue with digitalis for a year, then to reduce the dose before eventually omitting treatment. If a relapse or deterioration occurs at any time digitalis should be given for at least a year afterwards.

Conclusion

Primary myocardial disease is less rare than has been believed. The diagnosis can be made more frequently in practice if the clinical picture is familiar, if cardiomegaly is carefully sought, and if the value of electrocardiography in infancy is appreciated. The clinician's task is important, despite the gaps in our knowledge of aetiology and pathology, for on diagnosis depends what may prove to be life-saving treatment.

To Professors A. V. Neale and C. Bruce Perry, and to Drs. F. S. W. Brimblecombe, B. D. Corner, H. Jolly, D. Vulliamy and B. Webb, I gratefully acknowledge my

indebtedness for allowing me to see cases and for making records and material available.

Addendum

Since the above report was written, 12 cases of anomalous left coronary artery have been reported from the Johns Hopkins Hospital (Sabiston, Pelargonio and Taussig, 1960). After ligation of the anomalous artery, together with de-epilicardiazation, three cases have survived (one to the age of 4 years).

References

Apley, J., Corner, B. D. and Gibson, T. C. (1955). Paroxysmal tachycardia in infancy. *Arch. Dis. Childh.*, **30**, 517.
——, Horton, R. E. and Wilson, M. G. (1957). The possible role of surgery in the treatment of anomalous left coronary artery. *Thorax*, **12**, 28.
Dennis, J. L., Hansen, A. E. and Corpening, T. N. (1953). Endocardial fibroelastosis. *Pediatrics*, **12**, 130.
Keith, J. D. (1959). The anomalous origin of the left coronary artery from the pulmonary artery. *Brit. Heart J.*, **21**, 149.
——, Rowe, R. D. and Vlad, P. (1958). *Heart Disease in Infancy and Childhood*. Macmillan, New York.
Nadas, A. S. (1957). *Pediatric Cardiology*. Saunders, Philadelphia.
Rosenbaum, H. D., Nadas, A. S. and Neuhauser, E. B. D. (1953). Primary myocardial disease in infancy and childhood. *Amer. J. Dis. Child.*, **86**, 28.
Sabiston, D. C., Jr., Pelargonio, S. and Taussig, H. B. (1960). Myocardial infarction in infancy. The surgical management of a complication of congenital origin of the left coronary artery from the pulmonary artery. *J. thorac. cardiovasc. Surg.*, **40**, 321.

HYPERVITAMINOSIS D WITH OSTEOSCLEROSIS

BY

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Administration of vitamin D in high dosage produces extraosseous calcification, renal failure and usually hypercalcaemia, with a characteristic set of symptoms (Jeans, 1950). Its effects on bone have been alluded to in a number of publications (Jeans, 1950; Ross, 1952; Debré, 1948; Anning, Dawson, Dolby and Ingram, 1948; Ross and Williams, 1939; Tumulty and Howard, 1942; Danowski, Winkler and Peters, 1945; Howard and Meyer, 1948; Freeman, Rhoads and Yeager, 1946; Thatcher, 1931). In adults the characteristic roentgenologic bone finding is rarefaction. In children rarefaction is also reported, but with the additional finding of increased density of the zone of provisional calcification, and periosteal thickening (Ross, 1952).

The following case report demonstrates that excess ingestion of vitamin D may be accompanied by a severe degree of osteosclerosis, which is reversible, in addition to its better known effects.

Case History

A 5½-year-old white boy was admitted to the Orthopaedic Hospital Clinic complaining of pain in the right leg and flat feet. At the age of 3 he was considered elsewhere to have rickets on the basis of a 'peculiar feeling to the bones of the skull' and radiographs of the wrists. He was given two capsules of vitamin D daily, each containing 50,000 units, in addition to two tablespoons or more of cod liver oil and multivitamin drops. A few months after this he developed nausea and nontender recurrent lumps the size of half a lemon, over both tibias. His physician prescribed vitamin C and the lumps disappeared. In addition to the vitamin therapy at home, he was given a teaspoonful of cod liver oil daily at nursery school. After nine months of this therapy he became irritable, restless and nauseated, and the vitamins were stopped by the family. At the age of 4½, a diagnosis of rheumatic fever and anaemia was made and treatment was started with ferrous sulphate and sodium salicylate. His appetite was good, but he continued to be irritable and restless, sleeping only five hours at night. During the ensuing year his refusal to participate in school activities was ascribed by his teacher to stiffness in the extremities.

His birth weight was 8 lb. 8 oz. He was the son of a young woman who was married and separated before the child was born. Labour and delivery were normal. He was breast fed for eight months. He sat at 5 months, stood at 10 months, and walked at 11 months. His first tooth erupted at 4 months.

He was brought up chiefly by the mother's parents, while the mother worked. At an early age he had a tonsillectomy, adenoidectomy and circumcision. He also had measles.

Physical examination revealed an alert, hyperactive, well-developed and nourished white boy (Fig. 1). There was increased A-P diameter of the head with a suggestion of frontal and parietal bossing. The eyes, ears, nose and throat were normal. Dentition was normal, and the teeth appeared healthy. The thyroid gland was not

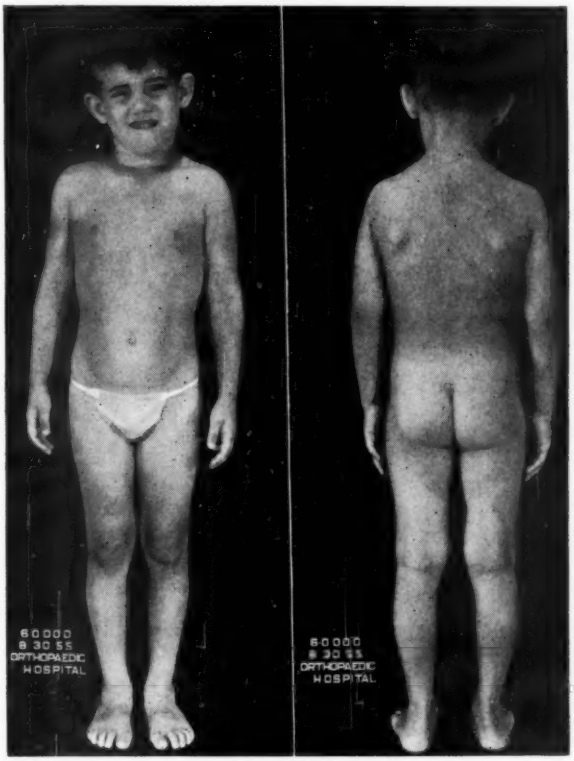

FIG. 1.—The patient at 5½ years of age.

FIG. 2.—Radiograph at initial examination. Note alternating bands of decreased and increased density at ends of radius and ulna.

FIG. 3.—Skull showing generalized increase in density.

palpable. The thorax showed beading of costochondral junctions. The heart, lungs and abdomen showed no abnormalities. The genitalia were normal for a boy of 5. The testes were in the scrotum.

The epiphyseal regions of the long bones were stocky and broad. There was no tenderness or pain. There was eversion of the os calcis and loss of the longitudinal arch bilaterally. There was some spasm of the left rectus femoris muscle and 20-degree flexion contractures of the knees. The skin was clear. There were no palpable calcific deposits anywhere. There was a healed ecchymosis on the lateral aspect of the right thigh.

A complete blood count showed 3·70 million erythrocytes, 12·8 g. haemoglobin, 10,400 leucocytes, with 40% polymorphs, 52% lymphocytes, 4% eosinophils, and 4% transitional forms. Urine analysis showed pale yellow urine of specific gravity 1,005, acid reaction, no sugar, acetone, albumin or formed elements. Urine calcium was 0·19 g. in a 24-hour volume of 1,750 ml. Serum calcium was 17 mg. per 100 ml., phosphorus 5·2 mg. per 100 ml., alkaline phosphatase 19 King-Armstrong units, acid phosphatase 5·3 King-Armstrong units, and protein-bound iodine 6·8 μg. %. Radiographs showed generalized increase in density of the bones. Alternating bands of decreased and increased density were present in the metaphyses, best seen at the wrist (Fig. 2). The cortices of the metatarsals, metacarpals, and phalanges were thickened. Metaphyseal areas were a little wider than usual and remodelling had not proceeded normally. There was some encroachment on the medullary canals at the ends of the long bones and in the shaft, caused possibly by thickened cortex. The base of the skull and cranial vault were increased in density (Fig. 3). The petroclinoid ligaments were heavily calcified. Periarticular calcifications were present about the feet, hips, hands, ankles and shoulders. Kidney shadows were dense but not markedly so. The lumbar spine showed dense and square appearing vertebral bodies (Fig. 4). Intervertebral discs were not calcified. Soft tissue calcification or periosteal new bone could be made out along the sternum.

A chest film made two years previously showed no abnormalities in the lung fields, and normal bone density. Films of the wrists and skull made one and a half years previously showed normal bone density (Figs. 5-6). Zones of provisional calcification were maintained. The epiphyseal lines were not widened. Bony maturation corresponded satisfactorily with the given chronological age of 4 years. The skull showed no abnormalities. There was no roentgen evidence of rickets.

The family was instructed to stop administering vitamin D and presumably did so. They did not return for follow-up observation and care except sporadically, as he was under private care for general paediatric supervision.

Radiographs were obtained at seven, eight and 10 months after initial examination. An antero-posterior view of the pelvis after seven months showed a thin zone of decreased density about the pelvic bones, probably representing new growth (Fig. 7). Femoral

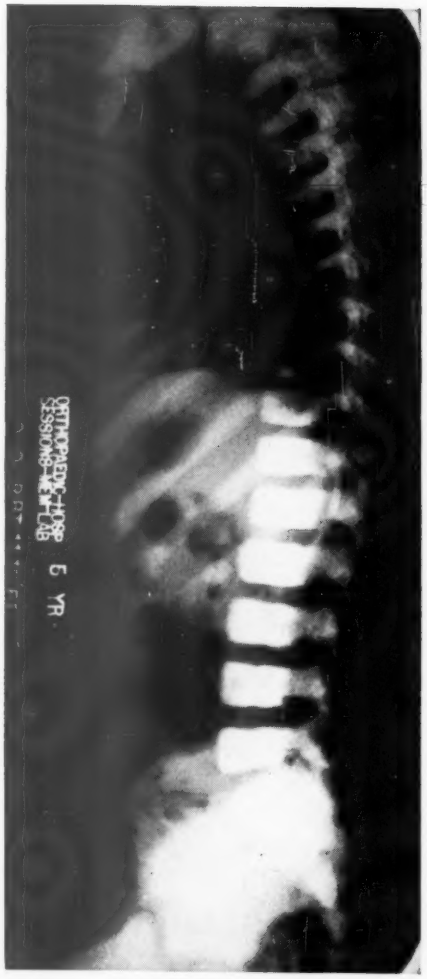

FIG. 4.—Note the dense square-appearing vertebral bodies.

FIG. 5.—Normal appearing bone structure at the age of 4.

FIG. 7.—Pelvis seven months after discontinuing vitamin D.

FIG. 6.—Normal appearing skull at the age of 4.

FIG. 8.—Note new bone growth at ends of radius and ulna.

arteries were seen to be delicately outlined by calcium. A month later, films of the wrists showed widened zones of relatively decreased density about the ends of the long bones, presumably representing bone laid down since the patient was taken off massive doses of vitamin (Fig. 8). Periarticular calcification persisted. Bony maturation was about 4 years, definitely retarded for the chronologic age of 6 years and 2 months. Two months later zones of lessened density were seen about the metaphyses adjacent to the knees and ankles (Fig. 9a).

FIG. 9a.—Lower extremities at 5 years.

Fifteen months after our first examination, he was taken to his private paediatrician, who kindly provided us with data concerning his course during the next several months. He was kept in hospital at this time because of fever, swelling of face and abdomen, and haematuria, after an upper respiratory infection. He had slight fever, tachycardia, a blood pressure of 180/120 mm. Hg, and moderate oedema of face and abdomen. Treatment was instituted with strict bed rest, penicillin and moderate salt restriction. Parenteral reserpine and 'apresoline' (hydrallazine) were given for one week, with a drop in blood pressure to 130/85 mm. Hg. An intercurrent viral gastro-enteritis was followed by loss of facial oedema and ascites. Blood pressure remained between 130/90 and 110/80 mm. Hg without further hypotensive drugs. His weight had dropped to 40 lb. from 48·5 lb. on admission. His urine which had many red cells on admission, cleared to 20-25 per h.p.f. and he was discharged home.

Radiographs during this period revealed bone density to be less than previously. Calcifications were present in the falx cerebri and tentorium. Periarticular calcifications were still evident about the hips. The transverse diameter of the heart was at the upper limit of normal. Renal shadows were moderately dense. The tip of the 12th rib was apparently fractured. Bony maturation was about 4 years, compared with the chronological age of 6 years and 10 months.

Laboratory studies during this period and for the next several months are tabulated (Table 1). The blood pressure remained near 120/90 mm. Hg on hypotensive therapy. The urine continued to show albumin, red blood cells and casts. The blood sedimentation rate and non-protein nitrogen remained elevated.

The family did not follow the rigid routine of bed rest prescribed, and sent him to school without medical permission.

When he was seen by the author one year after being in hospital under Dr. Woltmann, he was an alert, 7-year-old boy with a uraemic odour and marked pallor. Blood pressure was 190/130 mm. Hg. The fundus showed moderate crossing changes but no haemorrhages or papilloedema. Lungs were clear. The heart was enlarged to percussion and had loud tones of poor quality. There was a late diastolic sound suggestive of a presystolic murmur. The abdomen showed no abnormalities. There was no ascites or oedema. Skeletal survey by radiograph at this time showed continued loss of bone density (Fig. 9b). Bone of more normal density had been laid down since vitamin dosage had been discontinued. The overall decrease in density had been spectacular. Soft tissue calcifications were still demonstrated in the tissues about the hips. Chest film showed the heart to be moderately enlarged. The renal shadows had decreased in size and were increased in

TABLE 1
LABORATORY FINDINGS DURING 1957

Date (1957)	Urinalysis	Haemoglobin (g./100 ml.)	Non-protein Nitrogen (mg./100 ml.)	Sedimentation Rate (mm./hr) (Wintrobe)
February 28	4+ albumin; 10–13 R.B.C.; 3–4 W.B.C.; many casts	12	76	40
March 28	4+ albumin; 12–15 R.B.C.; 10–14 W.B.C.; many casts	13·4	76	44
May 16	3+ albumin; 8–10 R.B.C.; 10–12 W.B.C.; granular casts	13·4	72	39
September 12	4+ albumin; 6–8 R.B.C.; 10–12 W.B.C.; granular casts	10·7	103	92

density, although no definite calcifications were identified.

An electrocardiogram was within normal limits. Blood studies and urine analysis are tabulated (Table 2). A grave prognosis was given and a low protein diet omitting milk was advised. In spite of this, however, the family insisted he attend school if at all possible. The next few weeks saw development of widespread ecchymosis, oozing of blood from the nose, and increased depth of breathing with gallop rhythm. The family called in a physician living near them, who supervised his home care. He died soon after being readmitted to hospital.

Autopsy. Autopsy revealed small amounts of fluid in the peritoneal and pericardial cavities. The heart weighed 268 g. The left ventricle measured 14 mm. in thickness. There were some atherosclerotic changes in the first part of the aorta. The coronary ostia were patent. Both lungs were dark red and firm posteriorly, appearing juicy, bloody, and mucopurulent on cut section. The gastrointestinal tract showed haemorrhagic spots in the stomach and first portion of the duodenum. There was an intestinal intussusception about 6·5 cm. in length, approximately 90 cm. above the ileocaecal valve. The liver was abnormally heavy at 850 g. Cut surface showed fatty change. The spleen, pancreas and adrenals were normal.

Both kidneys were embedded in a small amount of fat. The right kidney weighed 47 g. (normal 74 g.) and the left kidney weighed 53 g. (normal 75 g.). On cut surface the capsule stripped with difficulty. After removal of the capsule the surface of both kidneys appeared granular. The pelvis appeared normal.

Lymphoid tissue was grossly normal. The thyroid showed cystic change. The parathyroid glands appeared normal. The bone marrow was deep red-brown in

TABLE 2
TERMINAL LABORATORY STUDIES

Laboratory Studies	Findings
Urinalysis	Sp. gr. 1,012, *p*H 6·0, albumin 4+; sugar negative, 15–25 W.B.C., 4–6 R.B.C., occasional epithelial cell, occasional broad coarse casts, occasional coarse granular cast, occasional broad W.B.C. cast
Complete blood count	Hb 5·9 g./100 ml., W.B.C. 10,900; polymorphs 65, lymphocytes 22, basophils 1, monocytes 9, eosinophils 3, haematocrit 18%
Serum creatinine	6·1 mg./100 ml.
Blood urea nitrogen	108 mg./100 ml.
Serum K	4·7 mEq/litre
Serum alkaline phosphatase	8·0 Bodansky units
Serum inorganic phosphorus	9·2 mg./100 ml. (5·3 mEq/litre)
Serum calcium	8·4 mg./100 ml. (4·1 mEq/litre)

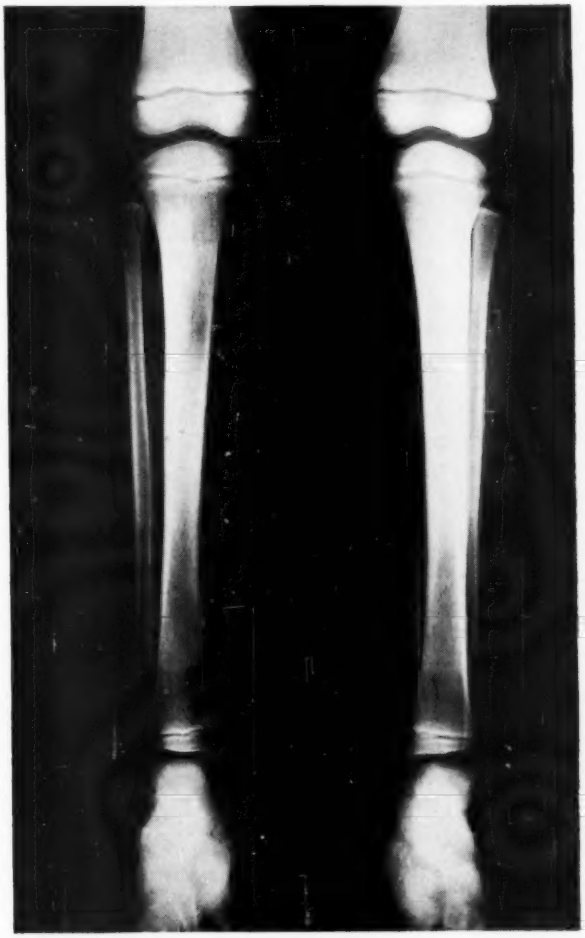

FIG. 9b.—Lower extremities at 7½ years, showing course of sclerotic bony process.

FIG. 10.—Autopsy section of kidney. (× 73.)

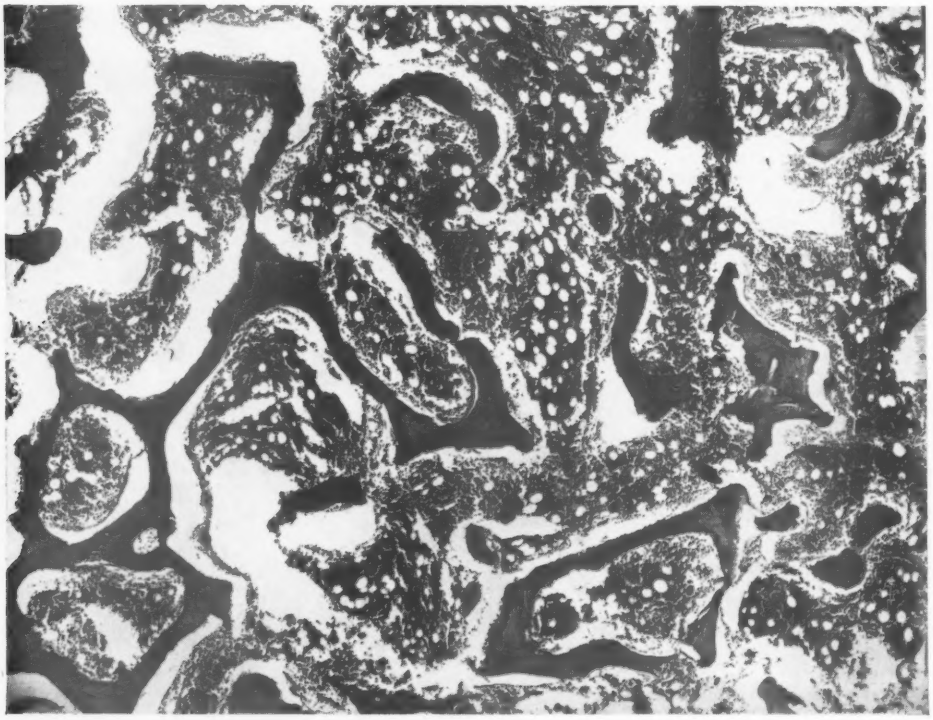

FIG. 11.—Autopsy section of bone marrow. (× 34.)

colour. The brain was grossly normal, but was increased in weight to 1,365 g. The pituitary gland was normal.

On microscopic section, the heart showed hypertrophy and coronary atherosclerosis. The lungs showed metastatic calcification of the alveolar wall and peribronchial tissue. There was uraemic pneumonitis. The gastrointestinal tract showed haemorrhage in the small intestine and multiple metastatic calcification of gastric glands. There was minimal fatty change in the liver. Metastatic calcification was present in the adrenal glands, but not in the spleen or pancreas. The pathologist's description of the kidney sections follows:

'Practically all glomeruli are fibrotic and there is very extensive atrophy of tubules. What glomeruli remain show at times adhesions and at times crescent formation. There is a marked interstitial fibrosis and inflammatory reaction with striking deposition of calcium throughout the renal parenchyma. Calcium is found in both cortex and medulla. At times it lies within tubular cells, at other times within glomeruli and most frequently appears to lie interstitially. There is extensive intimal proliferation of both small arteries and arterioles.' (See Fig. 10.)

The bone marrow (Fig. 11) showed osteoporosis. Parathyroid tissue was hyperplastic.

Discussion

Increased density of bone is seldom seen and always presents an interesting problem in diagnosis. The possibility of marble-bone disease was quickly dismissed when the serum calcium level was reported. It appeared highly likely that the excessive ingestion of vitamin D was the cause of his presenting complaints and striking findings. It is not possible to exclude hypervitaminosis A. Vitamins A and D are combined in most dose forms, and information regarding exact dose form is not available in the present instance.

That the excess deposit of mineral is actually a result of excessive vitamin ingestion seems likely in view of the following considerations. First, the history and findings apart from the skeleton are consistent with the known syndrome of vitamin D intoxication. Second, the dose and duration of ingestion of vitamin D were greatly excessive. Third, reported cases of vitamin D intoxication with bone demineralization were mostly older people and patients with rheumatoid arthritis. It is plausible to believe that skeletal maturity does not favour deposition of mineral salts. Furthermore, metabolic forces against skeletal mineralization exist in rheumatoid arthritis, an inflammatory disease with catabolic, or at least anti-anabolic effect on bone and other supporting structures.

It seems reasonable that a child's growing skeleton would react to a high concentration of circulating calcium by incorporating it in the skeleton at areas of epiphyseal and membranous growth. The distribution of excess mineral deposit in long bones is consistent with this type of orderly deposition. Known actions of vitamin D relate to improved absorption of calcium and phosphorus, rather than to specific effects at the level of bone mineralization. Thus it should be possible to correlate skeletal calcification with the level of serum calcium. A study of the ionized calcium level would have been valuable.

A striking parallel to the present case is seen in the cases reported as 'idiopathic hypercalcaemia' (Lowe, Henderson, Park and McGreal, 1954; Creery and Neill, 1954; Creery, 1953; Payne, 1952; Lightwood, 1952; Fellers and Schwartz, 1958; Fanconi, Girardet, Schlesinger, Butler and Black, 1952). The main clinical and laboratory features are similar, except for the onset and duration, and the presence of the 'elfin facies' and associated sequelae.

An interesting feature of the present case is the prompt reversal of bone density on discontinuance of vitamin D therapy. This began before evidence of renal failure appeared. Later progressive bone demineralization should properly be ascribed to renal failure with accompanying acidosis. A finding supporting this view is the presence at autopsy of osteoporosis in the bone sections, representing loss of more than the expected amount of bone substance. Closer observation of calcium metabolism might have changed the outcome. It is known that renal damage secondary to hypervitaminosis D is reversible. The presence of a constant steady stream of calcium from bone to blood stream was undoubtedly responsible for progressive unrelenting renal damage. It was not possible to test the effect of cortisone or other drugs on the serum calcium level.

The chief value of the present case report appears to be the demonstration of a mechanism for quantitative increase in bone mineral in humans. Many interesting studies could be planned on similar cases. It is hoped that the report of this case will stimulate others to make further careful observations in the rarely available similar situation.

Summary

A case report of a young boy who ingested large quantities of vitamin D over a period of one year demonstrates that reversible increase in bone density may occur, with severe calcinosis and fatal renal failure.

The extent and distribution of the osteosclerosis differs from that reported in vitamin D overdosage in children and resembles somewhat the picture seen in the severe cases of 'idiopathic hypercalcaemia'.

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References

Anning, S. T., Dawson, J., Dolby, D. E. and Ingram, J. T. (1948). The toxic effects of calciferol. *Quart. J. Med.*, **17**, 203.

Creery, R. D. G. (1953). Idiopathic hypercalcaemia of infants. *Lancet*, **2**, 17.

—— and Neill, D. W. (1954). Idiopathic hypercalcaemia in infants with failure to thrive. *Ibid.*, **2**, 110.

Danowski, T. S., Winkler, A. W. and Peters, J. P. (1945). Tissue calcification and renal failure produced by massive dose vitamin D therapy of arthritis. *Ann. int. Med.*, **23**, 22.

Debré, R. (1948). Toxic effects of overdosage of vitamin D_2 in children. *Amer. J. Dis. Child.*, **75**, 787.

Fanconi, G., Girardet, P., Schlesinger, B., Butler, N. and Black, J. (1952). Chronische Hypercalcämie, kombiniert mit Osteosklerose, Hyperazotämie, Minderwuchs und kongenitalen Missbildungen. *Helv. paediat. Acta*, **7**, 314.

Fellers, F. X. and Schwartz, R. (1958). Etiology of the severe form of idiopathic hypercalcemia of infancy: a defect in vitamin D metabolism. *New Engl. J. Med.*, **259**, 1050.

Freeman, S., Rhoads, P. S. and Yeager, L. B. (1946). Toxic manifestations associated with prolonged Ertron ingestion. *J. Amer. med. Ass.*, **130**, 197.

Howard, J. E. and Meyer, R. J. (1948). Intoxication with vitamin D. *J. clin. Endocr.*, **8**, 895.

Jeans, P. C. (1950). Vitamin D. *J. Amer. med. Ass.*, **143**, 177.

Lightwood, R. (1952). Idiopathic hypercalcaemia in infants with failure to thrive. *Arch. Dis. Childh.* (abstracts), **27**, 302.

Lowe, K. G., Henderson, J. L., Park, W. W. and McGreal, D. A. (1954). The idiopathic hypercalcaemic syndromes of infancy. *Lancet*, **2**, 101.

Payne, W. W. (1952). The blood chemistry in idiopathic hypercalcaemia. *Arch. Dis. Childh.* (abstracts), **27**, 302.

Ross, S. G. (1952). Vitamin D intoxication in infancy. Report of 4 cases. *J. Pediat.*, **41**, 815.

—— and Williams, W. E. (1939). Vitamin D intoxication in infancy. *Amer. J. Dis. Child.*, **58**, 1142.

Thatcher, L. (1931). Hypervitaminosis-D, with report of a fatal case in a child. *Edinb. med. J.*, **38**, 457.

Tumulty, P. A. and Howard, J. E. (1942). Irradiated ergosterol poisoning: report of two cases. *J. Amer. med. Ass.* **119**, 233.

SYSTEMATIC VENTRICULOGRAPHIC STUDIES IN INFANTS BORN WITH MENINGOMYELOCELE AND ENCEPHALOCELE*

THE INCIDENCE AND DEVELOPMENT OF HYDROCEPHALUS

BY

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Increasing experience and the introduction of new techniques in the treatment of congenital hydrocephalus demand its earliest possible recognition and knowledge of its natural history. By far the commonest type of congenital hydrocephalus is the one associated with a meningomyelocele or encephalocele. The presence of hydrocephalus in such infants should be suspected at birth, simply because the association is so common.

Present Investigation

An investigation was started on January 1, 1959, in the Children's Hospital, Sheffield. Its first purpose was to determine the incidence and degree of hydrocephalus in infants who were born with meningomyelocele or encephalocele, and to relate this incidence to various clinical features. The second purpose was to determine what effect, if any, early operation on the meningomyelocele would have on the development of hydrocephalus, and to determine the prognosis for those who had no hydrocephalus at the first examination. Its third purpose was to include those infants, who were found to have a hydrocephalus, in a controlled therapeutic trial. This paper deals with the results of the first two aspects of the investigations.

Methods

Infants with meningomyelocele or encephalocele were subjected to full clinical examination. The main method of investigation was ventriculography, which was often associated with dye penetration studies and sometimes with pneumoencephalography. The term 'hydrocephalus' in this paper refers to the radiological diagnosis of a pathologically distended ventricular system on ventriculography irrespective of any other feature. Ventriculography was performed through the right side of the anterior fontanelle. The depth of the cerebral cortex was measured by using a graduated needle for ventricular puncture. The cerebrospinal fluid pressure was measured in millimetres of water, while the infant was lying placidly, with the help of a sweetened dummy. This was followed by an injection of 20-40 ml. of sterile air. Radiographs were then taken in different positions of the head, including the head down position, to outline the whole ventricular system, as far as possible. Hydrocephalus was diagnosed if this system was unequivocally dilated, the angles of the lateral ventricles were rounded off, and the margins of the ventricles were convex. If hydrocephalus was found, it was arbitrarily graded into three groups. Grade 1 was the mildest, with considerable residual brain tissue, whereas in Grade III the cerebral cortex was, at the most, a few millimetres thick. Grade II fell between these two extremes (Fig. 1).

Case Material

This investigation is based on the study of 172 out of 214 infants who had been born with a meningomyelocele or an encephalocele, and who were admitted to the Sheffield Children's Hospital between January 1, 1959, and November 30, 1960 (Table 1). All were under 9 months of age on admission. There were 86 boys and 86 girls. Eighty-five infants were admitted on the first day of their life, 39 were between 2 and 7 days old, 25 were up to 8 weeks of age, and the last 23 were older (Table 2). These infants were admitted under the surgical care of Mr. Zachary, whose policy was to repair the lesion as soon as possible after admission. The excised segments were examined histologically by Dr. J. L. Emery. The diagnosis of meningomyelocele is based either on the presence of paralytic lesions in the segments involved by the spina bifida cystica or the presence of neural elements in the excised sac. In a few of the older infants the meningomyelocele had already been repaired at other hospitals, before they were transferred to us for the treatment of hydrocephalus. In 58 infants the meningomyelocele or encephalocele was repaired during the first day of life, in 60 between the

* Based on a paper delivered at a Joint Meeting of the Swedish and British Paediatric Association in Uppsala, in September 1959.

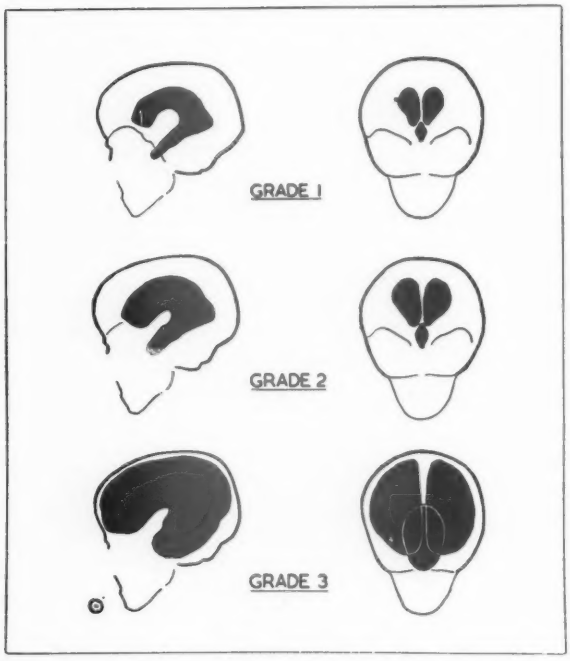

FIG. 1.—Diagrammatic representations of Grades 1, 2 and 3 hydrocephalus.

TABLE 1

214 CONSECUTIVE CASES OF MENINGOMYELOCELE AND ENCEPHALOCELE UNDER 9 MONTHS OF AGE

(Admitted January 1959–November 1960)

	No. of Cases
Ventriculogram not performed:	
Died before or soon after operation on meningomyelocele	30
Recent admissions, awaiting ventriculography	4
Survived, over 1 year of age, no apparent hydrocephalus	8
Total	42 (20%)
Ventriculogram performed:	
No hydrocephalus	30
Hydrocephalus	142
Total	172 (80%)

TABLE 2

172 CASES OF MENINGOMYELOCELE AND ENCEPHALOCELE

	Age			
	1st Day of Life	2–7 Days	1–8 Weeks	8 Weeks +
On admission	85	39	25	23
Meningomyelocele repaired*	58	60	26	18
Ventriculogram	—	4	126	42

* Ten were not operated on.

second and seventh days, in 26 during the next seven weeks, and in 18 at a later date. In 10 infants no attempt was made to repair the meningomyelocele (Table 2).

Ventriculography was performed in 17 infants before the repair of the meningomyelocele, in 80 within three weeks and in 75 more than three weeks after the operation (Table 3). Ventriculography was performed in 55% either before or at most three weeks after operation. Longer delays were usually due to late referral, the meningomyelocele having been repaired elsewhere, or to post-operative illness, including meningitis, which delayed these investigations. In seven infants ventriculography was again performed on a later occasion.

Forty-two other infants were admitted into hospital during the same period with spina bifida cystica; 30 of these died shortly after admission, and were never fit for ventricular studies. Eight were discharged from hospital soon after operation on their spina bifida cystica. None of these had paralytic lesions and there were no neural elements in the excised sac. They were all seen later and did not develop clinical hydrocephalus. These infants had a simple meningocele. Ventriculography was not ethically justifiable. Finally, four recent admissions have not yet reached the stage of ventriculography. These 42 infants are not included in this study.

Results

Ventriculography showed that 30 (17%) infants had either normal or only doubtfully enlarged ventricular systems and 142 (83%) infants had hydrocephalus (Table 4). Of these the hydrocephalus was trivial (Grade 1) in six, but the large majority had more serious ventricular dilatation, this being extreme in 51 (30% of 172 cases). Table 3 shows that the ventriculograms on infants who had no hydrocephalus were performed about the same interval after the surgical repair (average 25 days) as in those with hydrocephalus (average 29 days). The latter figure does not include 16 infants whose meningomyelocele was repaired after ventriculography, or not at all.

Head Circumference Related to Hydrocephalus.

Ventriculograms were performed on these infants irrespective of whether the size of their head was large or not at the time, and irrespective of whether there was fullness or bulging of the fontanelle, separation of the sutures or other signs of hydrocephalus. Table 5 shows that the head circumference of the 30 infants who had no hydrocephalus at the time of the ventriculography was below the 10th percentile at the time of examination in 20%, it was within the normal range* in 63% and was slightly above the 90th percentile in 17%. In contrast to this, 61% of the infants with hydro-

* For the purpose of this investigation the head circumference is regarded as normal if it falls within the 10th and 90th percentile.

TABLE 3

TIMING OF FIRST VENTRICULOGRAM IN RELATION TO REPAIR OF MENINGOMYELOCELE

Result of Ventriculogram	All Cases	Ventriculography						Average
		Before Repair		0–21 Days After Repair		22 Days or More After Repair		
		No.	%	No.	%	No.	%	
Normal ..	30	1	3	18	60	11	37	25
Hydrocephalus	142	16	11	62	44	64	45	29*
Total ..	172	17	10	80	47	75	43	

* Excluding 16 infants whose meningomyelocele was not repaired.

TABLE 4

RESULTS OF VENTRICULOGRAPHY IN 172 INFANTS WITH MENINGOMYELOCELE

(January 1959–November 1960)

	No.	%
No hydrocephalus	30	17
Hydrocephalus { Grade 1 ..	6	3
Hydrocephalus { Grade 2 ..	85	50
Hydrocephalus { Grade 3 ..	51	30

TABLE 5

HEAD CIRCUMFERENCE AT TIME OF FIRST VENTRICULOGRAM

Result of Ventriculogram	All Cases	Percentile					
		Below 10th		10th–90th		Over 90th	
		No.	%	No.	%	No.	%
No hydrocephalus ..	30	6	20	19	63	5	17
Hydrocephalus ..	142	7	5	48	34	87	61
Treated ..	61	2		22		37	
Control ..	54	3		21		30	
Advanced ..	27	2		5		20	

cephalus had an enlarged and often considerably enlarged head at this stage. It is more interesting to note, however, that the head circumference was within the normal range in 48 of the 142 hydrocephalic infants (34%) and in seven babies it was even below the normal in size, although the ventriculogram showed a considerable degree of hydrocephalus (Figs 2 and 3). The same data show that of the 92 infants whose head circumference was over the 90th percentile 87 (95%) had hydrocephalus. It is important to note, however, that of the 80 whose head circumference at this stage was normal or below the normal range, 55 (69%) had ventriculographic evidence of hydrocephalus (Table 6). It is clear from these figures that although an abnormally large head almost always indicates hydrocephalus, a normal or small head in infants with meningomyelocele or encephalocele certainly does not exclude hydrocephalus which is present in almost two-thirds of such cases.

Site of Meningomyelocele and Encephalocele and Incidence of Paraplegia Related to Hydrocephalus.

One infant had an anterior encephalocele (protruding through a cleft palate), and 15 had occipital encephaloceles. The meningomyelocele was cervical in two, thoracic in 10 and sacral in 15. The lumbar segment was involved in 129 infants (75%). These included 48 thoraco-lumbar, 51 lumbar and 30 lumbo-sacral meningomyelocele (Table 7). The site of the encephalocele or meningomyelocele

TABLE 6

HEAD CIRCUMFERENCE AT TIME OF VENTRICULOGRAPHY RELATED TO INCIDENCE OF HYDROCEPHALUS

Percentile	Total		No Hydrocephalus	Hydrocephalus	
Below 10th	13	80	6	7	55 (69%)
10–90th ..	67		19	48	
Over 90th ..	92		5		87 (95%)

TABLE 7

RELATION OF SITE OF MENINGOMYELOCELE OR ENCEPHALOCELE TO INCIDENCE OF HYDROCEPHALUS ON VENTRICULOGRAPHY

(January 1959–November 1960)

Site of Meningomyelocele or Encephalocele	All Cases			Hydrocephalus			No Hydrocephalus		
	No.		%	No.		%	No.		%
Palatal	1			—			1		
Occipital	15			11			4		
Cervical	2	43	25	—	27	63	2	16	37
Thoracic	10			7			3		
Sacral	15			9			6		
Thoraco-lumbar	48	129	28	46	115	96	2	14	4	11
Lumbar	51		30	75	44		89	7		14
Lumbo-sacral	30		17	25		83	5		17	
All	172		100	142		83	30		17

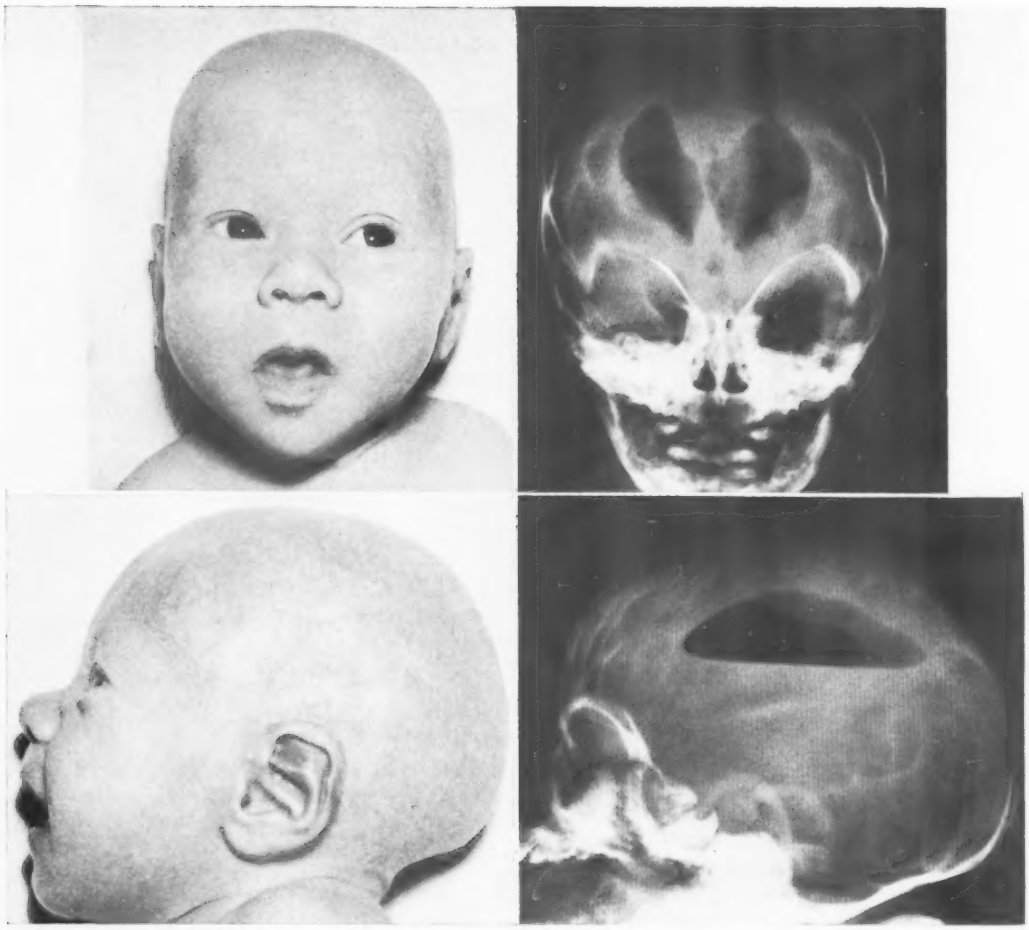

FIG. 2a and b.—Clinical photographs of an infant whose head circumference was normal and who showed no other clinical evidence of hydrocephalus.

FIG. 2c and d.—Ventriculograms of the same infant on the same day, showing Grade 2 hydrocephalus and craniolacunia.

had an important relationship to the incidence of hydrocephalus. The incidence of hydrocephalus according to the site of the lesion was as follows: thoraco-lumbar 96% (46 of 48), lumbar 86% (44 of 51), lumbo-sacral 83% (25 out of 30), occipital 73% (11 out of 15), thoracic 70% (seven out of 10) and sacral 60% (nine out of 15). When the meningomyelocele involved the lumbar region the incidence of hydrocephalus was 89%, as compared with an incidence of 63% when only other sites were involved.

TABLE 8

SITE OF MENINGOMYELOCELE AND ENCEPHALOCELE AND INCIDENCE OF PARAPLEGIA

(January 1959–November 1960)

Site	Paraplegia		No Paraplegia		Total No.
	No.	%	No.	%	
Lumbar (including thoraco-lumbar and lumbo-sacral)	108	84	21	16	129
All other sites	9	21	34	79	43
All	117	68	55	32	172

Cases with lumbar involvement are not only associated with a higher incidence of hydrocephalus, but usually they also have more serious neurological defects. The incidence of paraplegia in this group was 84% (108 out of 129), as compared with 21% in those 45 whose lesion did not involve the lumbar segments. Altogether 117 out of 172 infants had some partial or complete flaccid paralysis of their lower limbs (68%) (Table 8).

There was a close relationship between paraplegia and the incidence of hydrocephalus. Of 117 infants with paraplegia 109 (93%) had an associated hydrocephalus, as compared with an incidence of only

6[illegible]% among 55 infants without paraplegia (Table 9).

If these two sets of circumstances are combined (Table 10) it is seen that if an infant had a lumbar meningomyelocele with paraplegia, the incidence of an associated hydrocephalus was 96% (104 out of 108). If there was no paraplegia, or if the meningomyelocele did not involve the lumbar segments, then the chance of hydrocephalus was much less. Of 64 such infants 38 (60%) had hydrocephalus.

Prognosis. In this section those 115 infants will be considered who had been admitted up to and including March 1960. The survivors have been observed for a minimum of eight and a maximum of 23 months at the time of this analysis in December 1960.

TABLE 9

RELATION OF PARAPLEGIA TO INCIDENCE OF HYDROCEPHALUS ON VENTRICULOGRAPHY

(January 1959–November 1960)

	All Cases		Hydrocephalus		No Hydrocephalus	
	No.	%	No.	%	No.	%
Paraplegia	117	68	109	93	8	7
No paraplegia	55	32	33	60	22	40
Total	172	100	142	83	30	17

FIG. 3a and b.—Clinical photographs of another infant without clinical evidence of hydrocephalus.

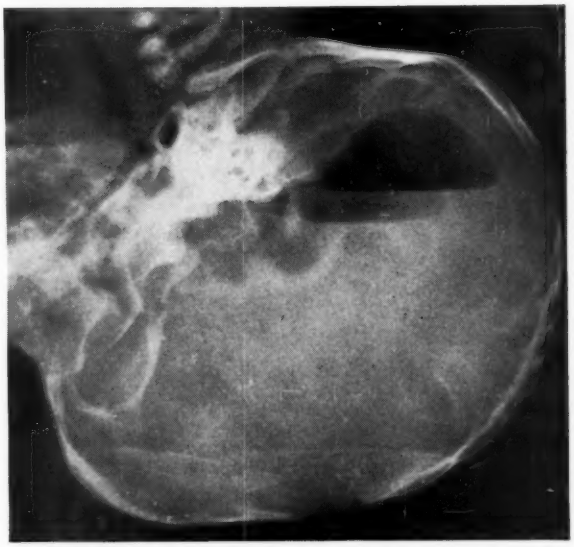

FIG. 3c and d.—Lateral views (one in the erect and one in the upside down position) of the same infant, on the same day, showing considerable dilatation of all parts of the lateral ventricles (Grade 2 hydrocephalus and craniolacunia).

TABLE 10

INCIDENCE OF HYDROCEPHALUS RELATED TO SITE OF MENINGOMYELOCELE OR ENCEPHALOCELE AND TO PARAPLEGIA

Site	Paraplegia	All Cases (No.)	Hydrocephalus	
			No.	%
Lumbar	+	108	104	96
Lumbar	−	21	11	52
All other sites	+	9	5	63
	−	34	22	

(*a*) *Infants with No Hydrocephalus.* It was of considerable importance to watch the physical and mental development of those infants who did not have hydrocephalus at the time of the ventriculography. Of the 22 followed for eight months or more, none developed clinically detectable hydrocephalus. One infant died at 8 months of age, and all the others are 1 year old or more. The head circumference at 1 year of age was slightly over the 90th percentile in three, it was normal (10th to 90th percentile) in 11 and it was only slightly or moderately below the 10th percentile in five. One of these infants had a most extensive thoraco-lumbar meningomyelocele which could be only partly repaired. Nevertheless, she has no paraplegia, and did not develop hydrocephalus. At 1 year of age her head circumference was only $17\frac{1}{4}$ in. (43·5 cm.) (Fig. 4a and b). She had a normal intelligence.

Finally, three infants with occipital encephaloceles became obviously microcephalic. One of these died in another hospital at 8 months of age with bronchopneumonia. The autopsy was not detailed, but no evidence of hydrocephalus was found. The head circumference of the other two extremely retarded infants was only 16 in. (40·5 cm.) at 12 months of age. One of these has very poor vision, and the developmental quotient of both is well below 50. Only these three infants with occipital encephalocele had an intellectual defect.

It would have been of great interest to repeat the ventriculogram in all 22 of these infants to prove that they did not develop hydrocephalus. In view of their good clinical progress this would have been unjustifiable. The ventriculograms, however, were repeated in three infants whose head circumference

FIG. 4a and b.—A 12-month-old infant whose extensive thoraco-lumbar meningomyelocele could only partly be repaired, but who had a normal ventriculogram. No hydrocephalus had developed by 18 months of age.

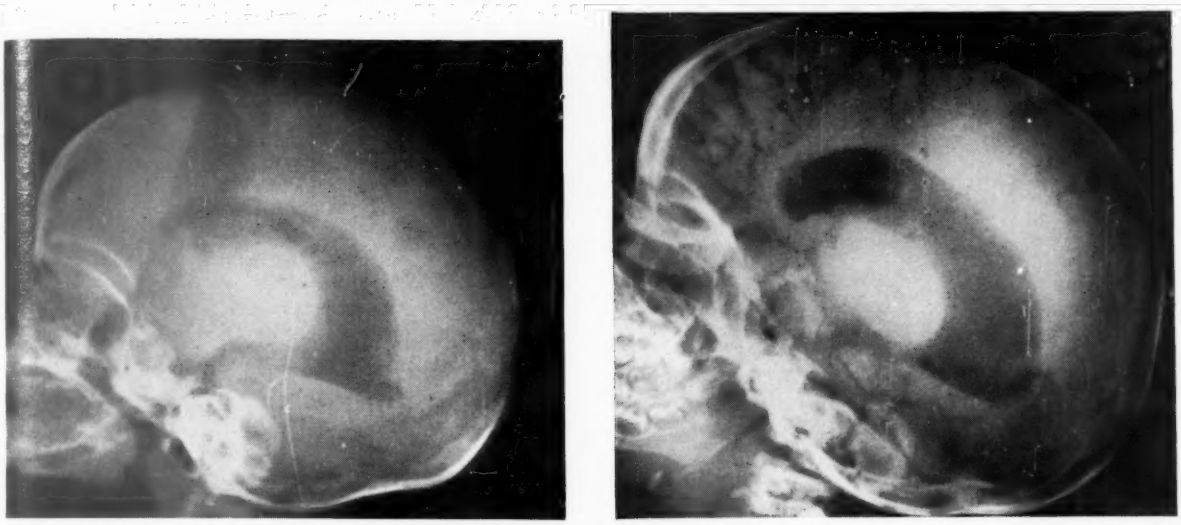

FIG. 5a and b.—Ventriculograms of an infant with a lumbo-sacral meningomyelocele repaired when she was 1 day old. The ventriculograms were performed at 6 and 35 weeks of age respectively.

exceeded the 90th percentile. None of them showed hydrocephalus at the second examination. Fig. 5a and b shows the ventriculograms of such an infant with a lumbo-sacral meningomyelocele which was repaired on the first day of life. The first ventriculogram was performed at 6 weeks, and the second at 35 weeks of age.

(*b*) *Infants with Hydrocephalus.* It is not within the scope of this paper to discuss in detail the outlook of the infants who had hydrocephalus. The natural history of their disease was influenced by various operative procedures, and more than half have been treated by a ventriculo-caval shunt. It is relevant, however, that 36 infants with hydrocephalus were not subjected to operative treatment immediately after ventriculography, but 11 were operated on later, because their head circumference showed a precipitous rise, well above the maximal normal range. There were only three infants in the 36 whose head circumference remained within the normal range (8%) and six whose head circumference pattern rose only moderately above the 90th percentile line (16%). All these had only slight or moderate hydrocephalus on ventriculography. Most of the moderate and all the severe cases of hydrocephalus showed a gross or precipitate increase in head size, resulting in obvious clinical hydrocephalus in 25 of the 36 (70%) before they reached their first birthday (Table 11).

Discussion

Before this study there were reports of large series of cases of spina bifida cystica (meningocele and meningomyelocele) and cranium bifidum (encephalocele) in which the site of the lesion was correlated with the incidence of hydrocephalus and in which the diagnosis of hydrocephalus was made either on clinical grounds or on autopsy evidence. The development of hydrocephalus either as a sequel to the operation on the meningomyelocele or independent of such procedures has also been discussed at length.

TABLE 11
HEAD CIRCUMFERENCE PATTERN OF INFANTS AFTER VENTRICULOGRAPHY

	Total	Micro-cephalic	1st–9th Percentile	Normal Range 10th–90th Percentile	95th Percentile	Grossly Enlarged	Died Early
Infants with no hydrocephalus	22	3	5	11	3	—	—
Infants with hydrocephalus who were not operated upon	36	—	—	3	6	25	2
Grade 1	2	—	—	1	1	—	—
Grade 2	26	—	—	2	5	17	2
Grade 3	8	—	—	—	—	8	—

Ingraham and Matson (1954) studied 1,433 cases of spina bifida cystica and cranium bifidum in the course of some 20 years. Of these, 187 were cases of encephalocele, 396 were considered to be simple meningoceles and 754 were meningomyeloceles. The proportion of simple meningoceles (in which the sac does not contain neural elements) was much higher than in the present series. The very low incidence of meningoceles in our material corresponds well with the series of Laurence (1960) who found only 9% of cases of meningocele in a series of 407 cases of spina bifida cystica seen in London.

In this series the incidence of hydrocephalus, as shown by ventriculograms, was closely linked with the site of the meningomyelocele. This observation is similar to that of Laurence, who estimated that the overall incidence of hydrocephalus in his series was 62% (based presumably on clinical signs and autopsy evidence). He too found that the incidence of hydrocephalus was highest when the meningomyelocele involved the lumbar (80%) or thoracolumbar region (70%) and less common in purely sacral (50%) or thoracic (43%) lesions. Ingraham and Matson (1954) considered that internal hydrocephalus was probably present in some degree in almost all patients with the Arnold Chiari malformation and that the hydrocephalus was of the communicating variety.

There has been no conclusive evidence so far to show whether the hydrocephalus is an essential part of the developmental disorder, and is present at birth, or whether the hydrocephalus develops later during the first year of life possibly as a result of operative interference or of meningitis resulting from an ascending infection.

Macnab (1958), discussing 200 cases (a part of the 407 reported by Laurence in 1960), found that 32% showed evidence of hydrocephalus at birth, in 16% the onset was between the 2nd and 3rd months and in 7% progressive hydrocephalus only became evident after about one year of observation. The criteria of the diagnosis of hydrocephalus were not stated, and it seems that the diagnosis was based on clinical evidence. Schaffer (1960) stated that many meningomyeloceles were associated with hydrocephalus at the onset, while in some infants hydrocephalus made its appearance early and progressed speedily.

Our findings indicate that hydrocephalus is frequently present in those infants whose head is not enlarged at the time and who show none of the other clinical signs which are accepted as evidence of hydrocephalus. We found this in 55 (39%) out of 142 infants with hydrocephalus. A similar observation on a smaller scale was made 20 years ago by Shapiro and Tosti (1940) who found ventriculographic evidence of hydrocephalus in six consecutive infants before the operation on their meningomyeloceles and whose head circumferences were normal at the time of the examination.

The ventriculograms in this series were performed on very young infants, either before or very soon after the repair of the meningomyelocele or encephalocele. No hydrocephalus developed subsequently in any infant who showed no hydrocephalus at this examination, in spite of the repair of their meningomyelocele or encephalocele. It has been shown that hydrocephalus, therefore, is an integral part of the clinical syndrome and is probably present right from the beginning in all those infants who subsequently develop clinical signs of the condition. In a very few cases the hydrocephalus remains subclinical throughout, but in the large majority this becomes manifest within the first two months of life. In view of these observations it is hardly necessary to discuss the mechanism of the development of the hydrocephalus following operative removal of the meningomyelocele. Nevertheless, Ingraham and Matson (1954) may well be right in their judgment that in some cases of meningomyelocele the associated Arnold-Chiari malformation in which the cerebrospinal fluid circulation is impaired only to a minor degree, may be disturbed by removal of the meningomyelocele. The operation may precipitate a more severe degree of obstruction of the cerebrospinal fluid's pathway and this may be followed by acute or slowly progressive hydrocephalus. They consider that this is the cause of the hydrocephalus after surgery, and not the decrease in the available absorptive surface, resulting from the removal of the sac. I would like to modify this view by suggesting that even in these cases the hydrocephalus was already present at the time of the removal of the sac, but that its progression to clinical hydrocephalus might have been accelerated.

It is possible, of course, for hydrocephalus to develop in those infants who did not have hydrocephalus before, or whose hydrocephalus was of trivial degree, if they should develop a pyogenic meningitis. This unfortunately is a common complication of meningomyelocele and may well occur in the mildest cases with disastrous results. In Macnab's (1958) series of 200 cases the incidence of meningitis was 18%. The meningitis usually occurs very early, and is often fatal. In this study, ventriculograms were either never performed in these infants or were done only after recovery from the meningitis, by which time evidence of gross hydrocephalus was usually available. Pyogenic

meningitis will, of course, also aggravate existing hydrocephalus. This has been shown in several infants in this series.

Summary and Conclusions

The following conclusions can be drawn from this investigation: (1) There is an 80% incidence of hydrocephalus in association with meningomyelocele and encephalocele in infants. This hydrocephalus can usually be detected in the first few days or weeks of life, even if the size of the head is not larger than normal, and other signs of increased intracranial pressure are not present. (2) The incidence of hydrocephalus is far higher in infants whose meningomyelocele involves the lumbar region, than when it involves other sites, and is far higher if there is associated paraplegia; 96% of infants with paraplegia and a lumbar meningomyelocele, and 95% of infants whose head circumference was over the 90th percentile in the first few weeks of life had radiologically demonstrable hydrocephalus. (3) There is no evidence that repair of the meningomyelocele in the early neonatal period influences the development of hydrocephalus. No infant who did not have hydrocephalus at the first examination developed clinical or other evidence of hydrocephalus during a period of follow-up lasting up to 23 months. (4) It is desirable to perform routine ventriculography in babies with meningomyelocele as soon as possible after birth. This is of great prognostic value and is useful as a guide to treatment.

I have great pleasure in thanking Mr. R. B. Zachary for his constant co-operation and for making this investigation possible, Dr. T. Lodge and Dr. R. G. Grainger for the radiographs and help in their interpretation; and many paediatricians from a wide area who are kindly referring their cases to us; Mr. P. Rickus for the photographic work, and many resident doctors and the nurses who bear the brunt of the day-to-day care of these difficult patients, and Professor R. S. Illingworth for his critical comments.

References

Ingraham, F. D. and Matson, D. D. (1954). *Neurosurgery of Infancy and Childhood.* Thomas, Springfield, Illinois.

Laurence, K. M. (1960). The natural history of spina bifida cystica. *Proc. roy. Soc. Med.*, **53**, 1055.

Macnab, G. H. (1958). Spina bifida cystica. In *Recent Advances in Paediatrics*, ed. D. Gairdner, 2nd ed., chap. 7, pp. 201-13. Churchill, London

Schaffer, A. J. (1960). *Diseases of the Newborn.* Saunders, Philadelphia.

Shapiro, B. and Tosti, V. G. (1940). Ventricular dilatation in spina bifida. *J. Pediat.*, **16**, 318.

ACCIDENTAL POISONING IN CHILDREN

BY

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In a statement by the United States Secretary of Health an estimate was made that in that country there were 600,000 non-fatal and 500 fatal poisonings of children annually (Flemming, 1960). Papers by Jacobziner and Raybin (1956) and Kubryk and McKenzie (1958) discuss the problem of poisoning of children in the United States and Canada respectively. This paper shows the position in England and Wales and is based on the morbidity and mortality data available in the General Register Office.

Cases Treated in Hospital

In 1958 the Hospital In-patient Enquiry of England and Wales collected data relating to 10% of all discharges from National Health Service hospitals (excluding mental hospitals). From these data 1,000 consecutive records of poisoning were extracted; 218 related to children under 15 years of age. The subsequent analysis in this section is based on these cases. The age and sex distribution is shown in Table 1.

For all age groups, except the two extremes, cases were seen more frequently among boys than girls. Although only rarely were details available concerning intention, it seems fair to assume that the great majority resulted from inquisitiveness in its broadest sense and could therefore be labelled as accidental. Poisoning among children admitted to hospital is shown to be commonest between 1 and 3 years of age. Over 3 it is relatively uncommon. As these data relate to children admitted to hospital it does not necessarily follow that cases of poisoning are infrequent in the older child, for once a child can talk the amount taken can usually be elicited and cases treated accordingly, often without hospital admission.

TABLE 1

AGE AND SEX DISTRIBUTION OF 218 CHILDREN ADMITTED TO HOSPITAL WITH POISONING

Sex	Age (years)							Total
	0–	1–	2–	3–	4–	5–	10–14	
Males ..	4	47	42	14	9	16	6	138
Females	5	29	19	10	4	2	11	80
Persons ..	9	76	61	24	13	18	17	218

Table 2 shows the nature of poison taken according to the age of the child. A very approximate estimate of 4,100 as the annual number of discharges from hospitals in England and Wales is also given. This was calculated by multiplying up the Hospital In-patient Enquiry data to give a national total. As classified, almost half the cases of poisoning resulted from the ingestion of pills, tablets, etc. 2-year-olds being most frequently affected. Other medical products consisted largely of liniments and

TABLE 2

AGE DISTRIBUTION AND POISON INVOLVED, AMONG CHILDREN ADMITTED TO HOSPITAL, AND ESTIMATED ANNUAL NUMBER OF DISCHARGES IN ENGLAND AND WALES

	Age (years)							Total Under 15 years	Estimated Number of Discharges in England and Wales
	0–	1–	2–	3–	4–	5–	10–14		
Pills, tablets, etc.	2	29	36	16	8	3	11	105	1,970
Other medical products	1	5	6	3	1	—	—	16	300
Household substances	4	38	16	2	1	6	3	70	1,320
Berries, seeds, etc.	—	—	1	1	1	5	—	8	150
Coal gas	1	—	—	—	1	1	1	4	30
Other and ill-defined substances ..	1	4	2	2	1	3	2	15	280
Total	9	76	61	24	13	18	17	218	4,100

liquid medicines, although a suppository was eaten in one case, and an inhalant capsule in another.

The most frequent cause of poisoning was the group of household substances, responsible for one-third of the admissions. Most commonly the child was in its second year.

Berries and plant substances were responsible for only eight admissions, usually in older children. Laburnum seeds were incriminated in four cases.

There were no deaths among this series of cases, although during 1958 there were 44 deaths of children in England and Wales as a result of accidental poisoning (see below).

Poisoning by Pills, etc. As shown by Table 3, the commonest drugs taken accidentally by children and resulting in admission to hospital were members of the aspirin group. Forty-four patients were admitted for this reason, 20% of all cases in the series. In seven instances the children were kept in hospital for more than three days.

The next most common cause of poisoning was the barbiturates, with 28 cases. Details of the type of barbiturate were not recorded sufficiently often for any worthwhile analysis to be made. It is noteworthy that the five children kept in hospital for more than three days with barbiturate poisoning were all girls and all aged 13 or 14. These may have been suicidal attempts, although this was only specifically stated in one case.

Iron preparations were responsible for seven cases, six of them children under 5 years. Phenolphthalein was responsible for four cases; it is an ingredient of laxative chocolate.

Among cases of poisoning by other substances, the two children staying in hospital for more than three days were a child of 2 who had taken some vitamin E and a child of 13 with phenytoin sodium poisoning.

Poisoning by Household Substances. Table 4 shows the wide selection of household substances responsible for the poisoning of children. Turpentine, paraffin, and disinfectants stand out as the most frequent cause of admission and the first two were also responsible for a large proportion of cases staying more than three days in hospital. This may have been because of the potential danger involved rather than the severity of the illness. Only two children, both having ingested paraffin, stayed in hospital for more than two weeks.

Cases Treated in General Practice

Besides those children taken to hospital other cases of poisoning that occur include those treated at home and those that die before reaching hospital.

TABLE 3

TYPE OF PILL OR TABLET INVOLVED IN POISONING OF CHILDREN ADMITTED TO HOSPITAL, BY AGE OF CHILD, DISTINGUISHING THOSE CASES KEPT IN HOSPITAL FOR MORE THAN THREE DAYS

Substance	All Cases			Cases with Duration of Stay Over Three Days		
	Age (years)			Age (years)		
	0–	5–14	Total	0–	5–14	Total
Aspirin and salicylates	42	2	44	5	2	7
Barbiturates	20	8	28	0	5	5
Iron preparations	6	1	7	0	0	0
Phenolphthalein	4	0	4	0	0	0
Other substances	19	3	22	1	1	2
Total	91	14	105	6	8	14

The number of cases of poisoning among children seen by general practitioners is unknown, but can be very approximately estimated at 8,000 (data from Logan, 1960). No series is known that is large enough for any estimate to be made of the type of poison implicated. If it is assumed that none of those cases in hospital were seen by general practitioners first, then the addition of the 4,000 cases requiring hospital treatment means that there is a maximum of about 12,000 cases of poisoning that require some form of skilled medical treatment in one year. Cases treated by parents are, of course, not included; neither are those treated only as out-patients by hospitals. This represents a rate

TABLE 4

TYPE OF HOUSEHOLD SUBSTANCE INVOLVED IN POISONING CHILDREN ADMITTED TO HOSPITAL, BY AGE OF CHILD, DISTINGUISHING THOSE CHILDREN KEPT IN HOSPITAL FOR MORE THAN THREE DAYS

Substance	All Cases			Cases with Duration of Stay Over Three Days		
	Age (years)			Age (years)		
	0–	5+	Total	0–	5+	Total
Bleach	3	—	3	—	—	—
Brandy	1	—	1	—	—	—
Carbon tetrachloride	2	1	3	—	—	—
Caustic soda	—	1	1	—	1	1
Cosmetics	3	—	3	1	—	1
Creosote	1	—	1	—	—	—
D.D.T.	1	1	2	—	—	—
Detergents	1	1	2	—	—	—
Disinfectants	7	—	7	1	—	1
Dye	1	—	1	—	—	—
Ink, commercial	1	—	1	—	—	—
Mercury	1	—	1	1	—	1
Moth balls	1	—	1	—	—	—
Paint	1	—	1	—	—	—
Paraffin	14	2	16	6	—	6
Polish (floor)	1	—	1	—	—	—
Polish (furniture)	1	1	2	—	—	—
Polish (silver)	2	—	2	—	—	—
Rat poison	1	—	1	—	—	—
Scourer	1	—	1	—	—	—
Surgical spirit	1	—	1	—	—	—
Turpentine	16	2	18	5	—	5
Total	61	9	70	14	1	15

TABLE 5

DEATHS OF CHILDREN UNDER 15 IN ENGLAND AND WALES ATTRIBUTED TO ACCIDENTAL POISONING BY YEAR 1954–1958

I.C.D. No.	Type of Poison	1954	1955	1956	1957	1958
E870–E888	Solid and liquid substances	27	28	16	21	24
E890–E895	Gases and vapours	22	23	31	10	20
	Total	49	51	47	31	44

of 1·2 per 1,000 children under 15 per annum and is considerably less than the estimate made for the United States (11·2 per 1,000).

Deaths of Children from Poisoning

Fortunately the number of accidental deaths of children from poisoning is small. Table 5 shows the number for the years 1954-1958. There seems to have been little change in the number of deaths over this period (about 44 per year). Just over half the deaths were caused by solid and liquid substances. Almost all the deaths by gassing were due to coal gas poisoning.

Table 6 shows the nature of the solid or liquid poison causing death in the same period. As with the hospital admissions, aspirin and salicylates head the list as the commonest single cause of death. Iron preparations were responsible for 12 deaths, but it is interesting to note that none occurred in 1957 or 1958. Strychnine was responsible for 10 deaths. Among the other substances, lead caused 12 deaths, and paraffin and caustic soda four each. Death from poisoning was relatively rare over 5 years of age, and was particularly so with drugs.

TABLE 6

DEATHS OF CHILDREN IN ENGLAND AND WALES ATTRIBUTED TO ACCIDENTAL POISONING BY SOLID AND LIQUID SUBSTANCES, 1954–1958

I.C.D. No.	Type of Poison	Age (years)		Total
		0–4	5–14	
E871	Barbituric acid and derivatives	3	1	4
E872	Aspirin and salicylates ..	22	0	22
E874	Other analgesic and soporific drugs	6	1	7
E876	Strychnine	10	0	10
E878 (pt.)	Iron preparations	12	0	12
E870, E877, E878 (pt.)	Other and unspecified drugs ..	15	1	16
E881	*Petroleum products	5	0	5
E883	†Corrosives	5	3	8
E885	Lead and its compounds ..	11	1	12
E884, E886, E888	Other and unspecified solid and liquid substances ..	17	3	20
	Total	106	10	116

* Paraffin, four; petrol, one.

† Caustic soda, four; disinfectants, two; sodium cyanide, one; boric acid, one.

Discussion

Cases of poisoning among children admitted to hospital are of two overlapping types; those where the child has taken a quantity of poison sufficient to make hospital treatment necessary and those where the child has taken an unknown quantity of what may be an unknown poison and admission is desirable as an insurance against the development of serious symptoms.

By the fact that 86% of cases admitted to hospital stayed there for less than four days it appears that relatively few cases are of any great severity and many may be trivial. Despite this, each case remains a potential tragedy and this is emphasized by the fact that there are about 23 deaths per year in England and Wales from solid and liquid substances alone. There can be little doubt that nearly all were preventable. Attention has been focused in recent years (Jolly and Forrest, 1958), on the desirability of making pills less attractive to children. Laudable though this aim may be, the data presented here show clearly that it is the availability of poisons which is at least as, if not more important than their attractiveness. There can be few families in this country that do not have paraffin, turpentine or aspirins somewhere in the house and it is these three substances together which accounted for almost 36% of hospital admissions for poisoning in children, and aspirins were the commonest single cause of poisoning death. None of the household substances mentioned would be classed as attractive in the sense that sweets may be, although it is true that some of the liquids were probably kept in old lemonade bottles. Among the medicinal substances, the most inviting was probably the laxative chocolate although the iron preparations were mostly sugar-coated and some of the barbiturates may have been attractive on the grounds of colouring. Together these amount to 39 out of 218 cases, or 18%. Thus it seems clear that the prevention of poisoning lies particularly with parents and the various means of publicity by which they can be reached. Special emphasis should be laid on the fact that it is the toddler who is most at risk. In this connexion it is worth mentioning the work of Russell, MacKenzie and McPhail (1960)

who showed the pertinacity of children in opening cupboards and bottles protected by so-called safety devices.

Harmful substances, however unattractive they may seem to adults, must not be left where they can be reached by the inquisitive fingers of the young child.

Summary

In England and Wales there are approximately 8,000 cases of poisoning annually among children seen by general practitioners, 4,000 are admitted to hospital and there are 44 deaths.

Boys are more commonly affected than girls and the maximum incidence is between 1 and 3 years of age.

The commonest poisons leading to admission to hospital are aspirins, paraffin and turpentine. The commonest single cause of death is aspirin and salicylate poisoning.

The availability of a poisonous substance to a child is at least as important as its attractiveness.

References

Flemming, A. S. (1960). Accidental poisoning. *U.S. Publ. Hlth Rep. (Wash.)*, **75**, 91.

Jacobziner, H. and Raybin, H. W. (1956). Accidental poisonings in childhood and their prevention. *J. Pediat.*, **49**, 592.

Jolly, H. and Forrest, T. R. W. (1958). Accidental poisoning in childhood: An experimental approach to the prevention of poisoning by tablets. *Lancet*, **1**, 1308.

Kubryk, D. and McKenzie, A. C. (1958). Accidental home poisonings. *Canad. J. publ. Hlth*, **49**, 420.

Logan, W P. D. (1960). *Morbidity Statistics from General Practice*, Vol. II (occupation). General Register Office Studies on Medical and Population Subjects, No. 14. H.M.S.O., London.

Russell, I. H., MacKenzie, S. and McPhail, G. (1960). Accidental poisoning in young children. Experiments with some safety devices. *Med. Offr*, **103**, 256.

BOWEL INFECTION AND ACUTE APPENDICITIS

BY

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This paper seeks to correct the widely held belief that a clinical or bacteriological diagnosis of infective diarrhoea excludes the presence or development of acute appendicitis.

The work that is described was stimulated by isolated incidents that occurred between 1950-1955: these are summarized in Table 1. In that period nine children had appendicectomies either when a bowel infection was present or before such an infection became manifest in the post-operative period: at operation four out of these nine cases were found to have acute appendicitis. A preliminary communication on the thesis of this paper was read at this hospital at a Summer meeting of the Paediatric Section of the Royal Society of Medicine in 1957 (Rogers, 1957).

Because of the findings shown in Table 1 an investigation was organized to inquire into the role of bowel infection as a factor in the aetiology of acute appendicitis: it was quite fortuitous that our planned project was started in January 1956, when a pandemic of Sonne dysentery in England was beginning.

Investigations

Main Investigation, 1956. In 1956 at the Children's Hospital Birmingham, there were 250 appendicectomies. The patients concerned represent 4·4% of a total of 5,730 patients admitted that year. Of these, 160 were suffering from acute appendicitis and all the appendices from them were examined, the distal two-thirds of each being sent for histological examination and the proximal one-third being used for bacteriological examination. When peritonitis was present, peritoneal pus or fluid was investigated. Examination and culture of the faeces were also performed. If no faeces was available a sheathed rectal swab was employed to obtain a true rectal specimen (Rogers, 1954). Twelve of the 160 patients were found to have *Shigella sonnei* in their appendices and it was thought that most of these patients had dysentery due to that organism as well as acute inflammation of the appendix. Table 2 presents the main symptoms, findings at operation and bacteriological investigations of each of these 12 cases. There was, in addition, a girl (Case 13, Table 2) who developed acute appendicitis with abscess formation while she was suffering from a salmonella infection. The normal appendices removed from 20 patients, were also cultured by the same techniques and neither *Sh. sonnei* nor salmonellae were isolated.

Investigations, 1957-1960. The number of appendices which are now cultured has fallen and we appear to be having a situation comparable to that seen before the Sonne dysentery pandemic of 1956. But the bacteriological findings we have obtained have supported the evidence showing that salmonella or shigella bowel infection and acute appendicitis may be associated. The case histories of the patients in these years are summarized in Table 3.

Although the notifications of dysentery in England and Wales rose higher in 1960 than they were in 1956, the number in Birmingham did not rise. This is shown in Table 4, which presents the figures supplied by the City's Medical Officer of Health. The bacteriological findings in Birmingham are similar to those in other parts of England and Wales, where *Shigella flexneri* causes only about 2% of all the dysentery infection, the majority being caused by *Sh. sonnei*: if the *Sh. flexneri* infections of the mental hospitals are excluded, only 1% of the dysenteric infections in the general population are due to that organism (Carpenter, 1960). We were not surprised, therefore, when *Sh. sonnei* was the dysenteric organism most commonly found in the case of appendicitis.

In Glasgow dysentery infections caused by *Sh. flexneri* are not uncommon. The figures given in Table 5 are extracted from the Annual Report on the work at Ruchill Infectious Diseases Hospital, Glasgow (Annual Report on the work of the Infectious Diseases Hospital in the Western Region of Scotland, 1959). They demonstrate how, in a five-year period, the percentage of dysenteric infections

TABLE 1

Date	Sex and Age (years)	Days Before Admission		Operative Findings	Bacteriology
		Diarrhoea	Pain		
May, 1950	M/4	0	1	Normal appendix; appendicectomy	*Salm. enteritidis* two days after appendicectomy when diarrhoea developed
June, 1950	M/5	3	1	Gangrenous appendix with abscess	No culture of pus from abscess; *Sh. sonnei* from faeces
January, 1951	M/7	0	4	Normal appendix; appendicectomy	*Sh. sonnei* from faeces two days after operation
March, 1951	M/4	1	1	Acute appendicitis, appendix adherent to liver; appendicectomy	No culture of appendix; diarrhoea developed six days post operatively; wound suppuration, *Sh. sonnei* cultured from wound pus and from faeces
May, 1951	M/12	1	4	Normal appendix; appendicectomy	Diarrhoea occurred three days post operatively; *Sh. sonnei* cultured from faeces
July, 1952	M/10	0	1	'Congested appendix'; appendicectomy	Diarrhoea two days post operatively; *Salm. typhimurium* cultured from faeces
January, 1953	M/12	0	4	Normal appendix; appendicectomy	Diarrhoea two days post operatively; *Salm. typhimurium* cultured from faeces
March, 1953	M/5	0	Few hours	Acute appendicitis with general peritonitis; appendicectomy	No culture of peritoneal pus or appendix; 'routine' faeces on admission grew *Sh. sonnei*
September, 1953	F/1	7	7	Normal appendix; appendicectomy	One day post operatively *Sh. sonnei* cultured from faeces
February, 1954	F/4	0	3	Appendix very inflamed; pus in peritoneal cavity	Peritoneal pus grew *Sh. sonnei*
February, 1954	M/11	Three attacks of diarrhoea and vomiting in two weeks		Adherent and inflamed appendix	No culture of appendix; *Sh. sonnei* in faeces two days post operatively
December, 1955	M/8	1	0	Appendix very inflamed; peritoneal toilet necessary	*Sh. sonnei* in faeces post operatively
December, 1955	M/5	Constipated	2	Perforated appendix; appendix abscess	*Salm. derby* from peritoneal pus and post operatively from faeces

TABLE 2

Case No.	Date	Sex and Age (years)	Days Before Admission		Contact	Temperature (° F.) on Admission	Operative Findings*	Bacteriology
			Diarrhoea	Pain				
1	January, 1956	M/6	3	3	Mother and father had diarrhoea and vomiting three weeks before	103	General peritonitis	*Sh. sonnei* from appendix and sheath swab, not from peritoneal pus
2	February, 1956	M/6	3	½	None	100	Local peritonitis	*Sh. sonnei* from appendix and sheath swab
3	February, 1956	M/9	½	½	None	99	Local peritonitis	*Sh. sonnei* from appendix and sheath swab
4	February, 1956	M/5	14 intermittent	1	None	101	Local peritonitis	*Sh. sonnei* from sheath swab, not from appendix
5	March, 1956	M/8	1	2	None	103	General peritonitis	*Sh. sonnei* from appendix and sheath swab, not from peritoneal pus
6	March, 1956	F/5	5 intermittent	5	None	100·6	Local peritonitis	*Sh. sonnei* from appendix and sheath swab
7	April, 1956	M/5	2	2	None	100	General peritonitis	*Sh. sonnei* from appendix and sheath swab, but not from peritoneal pus
8	April, 1956	M/8	4	2	7 siblings, 2 recently had diarrhoea and vomiting	100	General peritonitis	*Sh. sonnei* from appendix only; not from peritoneal pus or sheath swab
9	April, 1956	M/12	2	2	None	100	Local peritonitis	*Sh. sonnei* from appendix and sheath swab
10	May, 1956	F/2	4 at onset	4	Mother had diarrhoea one week before	100	General peritonitis	*Sh. sonnei* from appendix only, not from sheath swab or peritoneal pus
11	May, 1956	M/8	5	1	None	99	Local peritonitis	*Sh. sonnei* from appendix only, not from sheath swab
12	June, 1956	M/9	2	2	Sister had diarrhoea and vomiting one week before	103	General peritonitis	*Sh. sonnei* from appendix and sheath swab only, not from peritoneal pus
13	August, 1956	F 17 mths	3 (vomiting only); diarrhoea occurred three days after operation	3	None	100	Retrocaecal abscess	*Salm. heidelberg* from appendix and sheath swab

Eleven of the 12 strains of *Sh. sonnei* were identified on the primary cultures and one was only isolated by selenite enrichment.

* 1 had acute appendicitis.

TABLE 3

Date	Sex and Age (years)	Days Before Admission		Operative Findings	Bacteriology
		Diarrhoea	Pains		
April, 1957	M/11	0	1	Ileo-ileal intussusception; 'injected' appendix; reduction of intussusception and appendicectomy	Appendix yielded *Sh. sonnei* by selenite enrichment only
April, 1957	M/8	0	1	Acute appendicitis; local peritonitis; appendicectomy	Appendix yielded *Sh. sonnei* on direct culture
October, 1958	M/5	5 hours	5 hours	Appendicectomy; appendix showed 'acute focal infiltration of all layers'	Both appendix and faeces grew *Salm. typhimurium*
April, 1959	F/6	1	1	General peritonitis; appendix gangrenous and perforated; partly 'walled off' by omentum	Mixed growth with *Sh. sonnei* on direct culture
July, 1959	M/4	7	1–2	Gangrenous perforated retrocaecal appendix lying in an abscess with faecolith	Mixed growth with a few *Sh. sonnei* on direct culture
August, 1959	F/7	6 ceased at 2	?	General peritonitis; gangrenous perforated appendix, partly 'walled off' by omentum	Rectal swab, peritoneal pus and appendix all yielded *Sh. sonnei* on direct culture
June, 1960	M/½	For 7 days, 14 days before admission	1	Ileo-ileal intussusception requiring resection of non-viable gut; appendix nearly involved in intussusception, so removed	*Sh. sonnei* grown from appendix whose histology showed oedema and some polymorph infiltration only

TABLE 4

NOTIFICATIONS OF DYSENTERY IN THE CITY OF BIRMINGHAM IN THE FIRST TWO QUARTERS, 1956–1960

Year	First Quarter					Second Quarter				
	Total Notified	No. Investigated	Organisms Identified			Total Notified	No. Investigated	Organisms Identified		
			Sh. sonnei	*Sh. flexneri*	None			*Sh. sonnei*	*Sh. flexneri*	None
1956	744	431	372	0	59	305	267	112	4	51
1957	250	207	87	56	64	143	104	62	6	36
1958	209	163	93	0	70	118	73	48	1	24
1959	194	60	49	1	10	284	45	29	1	15
1960	171	46	30	1	15	181	55	36	2	17

TABLE 5

DYSENTERY IN RUCHILL HOSPITAL, GLASGOW

Organism	1955		1956		1957		1958		1959	
	No.	%	No.	%	No.	%	No.	%	No.	%
Sh. sonnei	408	56	485	86	326	87	328	75	278	57
Sh. flexneri	323	44	78	14	48	13	107	25	206	43
Total	731		563		374		435		484	

due to *Sh. flexneri* was very much higher than is usual in England and Wales. In February 1959, a girl of 15, who had had diarrhoea for one day was admitted to the Royal Infirmary, Glasgow; *Sh. flexneri* was isolated from her faeces, but her abdominal pain increased and appendicectomy was performed. At operation an inflamed appendix was found, without any pus formation or peritonitis (Patrick, 1959).

Diagnosis

The differential diagnosis of acute appendicitis in children has been discussed at length by Williams (1947) and Brown (1956). Both these authors draw attention to the fact that the 'difficult case' is the patient who does not have abdominal pain as the presenting and predominating symptom; they point out that diarrhoea, contrary to time-honoured orthodox surgical teaching, is a very common alternative manner of presentation. This diarrhoea, associated with vomiting, may precede or concur with the abdominal pain.

Campbell and McPhail (1958) noted that 16% of 450 adult cases with acute appendicitis had a history of diarrhoea, whilst Brown (1956) found this symptom in 12% of 1,148 children suffering from appendicitis. Zachary Cope (1957) draws attention to the fact that appendicitis in children may be heralded by the passage of loose stools. While it is recognized that diarrhoea may occur late in the disease, indicating the presence of a pelvic abscess, little attention has been paid to the significance of

diarrhoea as an early symptom. In the 160 cases studied in 1956, diarrhoea was an early symptom in 28 (17·5%). Amongst these 28 cases, were the 12 who were subsequently found to be suffering from Sonne dysentery. In four of these 12 children with shigella infections, diarrhoea preceded the abdominal pain: in seven, abdominal pain occurred at the same time as the diarrhoea and in one the diarrhoea started after the pain. The child with salmonellosis was constipated until three days after operation, when diarrhoea developed.

Vomiting occurred as an early symptom in 118 of the 160 patients studied (73·3%) and in 10 of the 12 patients with Sonne dysentery.

The physical signs we have used in the diagnosis of acute appendicitis in our children have been essentially those evaluated and found reliable in adults by Campbell and McPhail (1958); moreover, we have not found that they differ when there is concomitant dysenteric infection.

All our patients were pyrexial, but their fever showed no unusual features. Those patients with localized infection had temperatures of 100° F. or below: those patients with general peritonitis had temperatures of 101° to 103° F.

When allowance is made for the natural apprehension of the very young, and if gentleness is used and care taken not to alarm a frightened child, the signs of tenderness, guarding and release pain, in the right lower quadrant of the abdomen, are as valid in children as in adults, and the same applies to rectal tenderness.

In some patients the diagnosis of appendicitis was delayed because of the clinical picture of infective diarrhoea, and it is noteworthy that six of the 12 cases with Sonne dysentery had general peritonitis.

Treatment

In the 160 cases described in this study, appendicectomy was performed with or without drainage. Patients with general peritonitis received intravenous therapy and gastrointestinal suction. The dysenteric infection was treated in 11 cases with oral streptomycin 0·5 g. b.d. for seven days. One child received oral phthalyl sulphathiazole 1 g. q.d.s. for seven days. The children were considered free of infection after specimens of faeces obtained on three consecutive days had been examined and found to be free from the presence of *Sh. sonnei* (Rogers, 1954).

Bacteriological Techniques

The fragment of appendix sent for a cultural examination was placed in a sterile 1-oz. screw-topped bottle: in the laboratory this was cultured as if it was pus (Rogers, Zinnemann and Foster, 1960), and also as if it was faeces (Rogers, 1954). Strains of *Sh. sonnei* and salmonellae were first identified by slide agglutination and then this identity was confirmed by tube agglutination using a centrifuge, a method which provides a quick confirmation of the slide agglutination result (Rogers, Dowse and Hall, 1959). Other routine confirmatory tests were made and the *in vitro* antibiotic sensitivity reactions of each strain were examined, but no attempt was made to phage or colicine type them during 1956. Some of the strains isolated in 1959-60 have been colicine typed, but no single type was found to be associated with appendicitis.

Discussion

Several authors described how either *Salm. typhi* or *Salm. paratyphi B* were isolated from the appendix or the peritoneal pus removed from patients with acute appendicitis (Mackenzie, 1903; Wilde, 1930; Hawkes, 1939; Storey, 1954), Rubenstein and Johnson (1945) reviewed the literature on the subject and reported that a boy of 14, who had been under their care, developed appendicitis whilst suffering from salmonellosis due to *Salm. newport*, and that a 42-year-old man had a gangrenous appendix removed when he had salmonellosis due to *Salm. oranienberg*. There have been fewer reports in which the association of shigellosis and acute appendicitis has been proved. Graham (1944) reported that amongst 550 American troops, with dysentery due to *Sh. newcastle*, four also suffered from acute appendicitis, the appendices showing catarrhal changes.

Rose (1945) described how a man of 30, who had clinical dysentery due to *Sh. flexneri*, developed appendicitis two weeks later: no dysentery organisms were isolated from the foul pus found at operation: another man of 29 had mild clinical dysentery and acute appendicitis, but at no time were shigellae isolated from his faeces: *Sh. shigae* were isolated from the pus found at operation. Cowan (1958) reported 10 cases of acute appendicitis occurring amongst 345 patients with mild clinical dysentery: no bacteriological investigations were made.

The changes in the pattern of Sonne dysentery, which have occurred since 1947, have been discussed by Taylor (1957): it is possible that this change might be due to new strains brought to England in the post-war years by returning troops and transient foreign visitors (*Lancet*, 1956), but this increasing frequency of Sonne dysentery makes it important for the association of dysentery and appendicitis to be appreciated in Great Britain.

Rendle Short (1935) wrote: 'Pain associated with diarrhoea . . . is unlikely to have surgical significance'. Burrill Crohn (1945) stated: 'Diarrhoea and appendicitis rarely concur and it is a safe rule that fever, tenderness, and even rebound tenderness, in the presence of diarrhoea are almost invariably due to an acute gastro-enteritis or ileitis', but he admitted that if there were conditions of epidemic or endemic dysentery, a diagnosis of acute appendicitis could be seriously considered.

Several writers (Kross and Schiff, 1940; Keeling, 1942; Rose, 1945; Keyes and Cook, 1946), have emphasized how difficult it is to differentiate between appendicitis and dysentery. Rubenstein and Johnson (1945) showed how the white cell count was of no value in making this differential diagnosis; we agree that there is often a polymorphonuclear leucocytosis in a patient who is dehydrated, which can easily occur when a child has dysentery.

Many authors recorded that faecoliths were present or there was evidence of previous damage to the appendix in the patients who had this dual pathology. Perry and Tidy (1918) suggested that the intestinal disturbance of dysentery was liable to cause irritation of a previously diseased appendix, and Rose (1945) noted the presence of a faecolith in both his patients who had acute appendicitis due to shigellosis, as did Widal (1913) in the appendix abscess of his patient who had paratyphoid fever. Macroscopic and microscopic examinations of the appendix of each of our cases showed acute suppurative inflammation, progressing in some cases to gangrene and perforation, and no evidence was found which did not support the view of Wangensteen and Bowers (1937) and Bowers (1939) that obstruction was the exciting factor in the development of acute appendicitis.

It was our opinion that mucosal oedema was the precipitating factor in the development of the *acute appendicitis*, as a partial obstruction then became complete. Enterogenous infection of the appendix by bacteria, which may be recognized pathogens, may account for a larger number of cases of acute appendicitis than we had hitherto believed, especially those in which diarrhoea is an early symptom. Such a theory might revive the 50-year-old beliefs of Aschoff that the exciting cause of acute appendicitis was mucosal infection (Aschoff, 1932).

The awareness of the association of infective diarrhoea and acute appendicitis, which we have in fact shown to exist, is essential if a correct diagnosis is not to be delayed. The risk of hospital cross-infections will be reduced if patients with acute appendicitis, who might also have dysentery, are admitted to isolation wards or barrier nursed, until the bacteriological investigations are completed. In this hospital any non-lactose fermenting enterobacteriaceae is examined to ensure that salmonellae and shigellae are always identified: we are not the first to consider this logical, for in 1945 Rubenstein and Johnson advocated that appendices should be cultured on selective media to allow salmonellae or shigellae to be isolated, and the interesting report of Hormaeche, Surraco, Peluffo and Aleppo (1943) make it obvious that this is also the rule in their laboratory.

Summary

The evidence collected in a children's hospital over a period of 10 years has shown that acute appendicitis may be precipitated by a bowel infection. Symptoms and signs suggestive of acute appendicitis demand operation, even though a bowel infection may be known to be present. It is considered that an appreciation of this possible dual pathology will help to prevent hospital cross-infection due to salmonellae and shigellae. Previously published literature on the subject has been reviewed and discussed.

We would like to express our gratitude to the surgeons of the Children's Hospital, Birmingham, for allowing us access to the patients under their care; to the resident clinical pathologists who have helped with this work; to Drs. Matthew Burn and E. L. Millar and Professor Tom Anderson for epidemiological information, and Drs. Henry Baar and Hugh Cameron for permission to use their histological findings.

References

Annual Report on the work of the Infectious Diseases Hospital in the Western Region of Scotland, 1959.

Aschoff, L. (1932). *Appendicitis: its Aetiology and Pathology.* Translated by G. C. Pether. Constable, London. (First published, 1912.)

Bowers, W. F. (1939). 'Appendicitis' with especial reference to pathogenesis, bacteriology and healing. *Arch. Surg.* (*Chicago*), **39**, 362.

Brown, J. J. Mason (1956). Acute appendicitis in infancy and childhood. *J. roy. Coll. Surg. Edinb.*, **1**, 268.

Campbell, J. A. and McPhail, D. C. (1958). Acute appendicitis. *Brit. med. J.*, **1**, 852.

Carpenter, K. P. (1960). Personal communication.

Cope, Z. (1957). *The Early Diagnosis of the Acute Abdomen.* Oxford University Press, London.

Cowan, D. J. (1958). Appendicitis and acute terminal ileitis during an outbreak of gastro-enteritis among British troops in Port Said. *Brit. med. J.*, **1**, 438.

Crohn, B. B. (1945). Acute appendicitis and diarrhea. *Gastroenterology*, **4**, 511.

Graham, W. H. (1944). Diagnosis of appendicitis with gastro-enteritis. *Milit. Surg.*, **95**, 296.

Hawkes, S. Z. (1939). Paratyphoid fever complicated by ruptured appendicitis. *Ann. Surg.*, **110**, 466.

Hormaeche, E., Surraco, N. L., Peluffo, C. A. and Aleppo, P. L. (1943). Causes of infantile summer diarrhea. *Amer. J. Dis. Child.*, **66**, 539.

Keeling, J. (1942). Salmonella septicaemia. A report of seven cases. *N.Z. med. J.*, **41**, 254.

Keyes, E. L. and Cook, M. M. (1946). Diagnosis of acute appendicitis in the presence of diarrhea. *Arch. Surg.* (*Chicago*), **52**, 429.

Kr[illegible]ss, I. and Schiff, F. (1940). Pseudosurgical syndromes produced by salmonella organisms. *Amer. J. dig. Dis.*, **7**, 176.

La[illegible]cet (1956). Leading article. 'More dysentery.' **2**, 878.

M[illegible]kenzie, H. W. G. (1903). Perforation in typhoid fever. *Lancet*, 2, 863.

Pa[illegible]ick, W. (1959). Personal communication.

Perry, H. M. and Tidy, H. L. (1918). A report on the investigation of an epidemic caused by bacillus aertryche. *Spec. Rep. Ser. med. Res. Comm.*, No. 24.

Rendle Short, A. (1935). Abdominal pain in children. *Brit. med. J.*, 1, 1157.

Rogers, K. B. (1954). Clinical pathology in general practice. Examination of faeces for infection and infestation. *Ibid.*, 1, 147.

—— (1957). The association of acute appendicitis with infective diarrhoea. *Proc. roy. Soc. Med.*, **50**, 1025.

——, Dowse, J. E. and Hall, J. T. (1959). Techniques used in the routine examination of specimens for the specific serological types of *Escherichia coli*. *J. clin. Path.*, **12**, 191.

——, Zinnemann, K. and Foster, W. P. (1960). The isolation and identification of Haemophilus spp. from unusual lesions in children. *Ibid.*, **13**, 519.

Rose, T. F. (1945). The clinical differentiation of appendicitis and the dysenteries. *Med. J. Aust.*, **2**, 72.

Rubenstein, A. D. and Johnson, B. B. (1945). Salmonella appendicitis. *Amer. J. med. Sci.*, **210**, 517.

Storey, G. W. (1954). The pathology of salmonella food poisoning. M.D. Thesis, Liverpool University.

Taylor, I. (1957). The changing epidemiology of Sonne dysentery. *Proc. roy. Soc. Med.*, **50**, 31.

Wangensteen, O. H. and Bowers, W. F. (1937). Significance of the obstructive factor in the genesis of acute appendicitis: an experimental study. *Arch. Surg.* (*Chicago*), **34**, 496.

Widal, F. (1913). Rapport sur un travail de M. Walther concernant *un cas d'appendicite paratyphique*. *Bull. Acad. Méd.* (*Paris*), **69**, 283.

Wilde, J. F. (1930). Acute appendicitis complicated with paratyphoid fever. *Brit. med. J.*, **1**, 16.

Williams, H. (1947). Appendicitis in the young child. *Ibid.*, **2**, 730.

A NEW TECHNIQUE IN EXCHANGE TRANSFUSION

BY

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In experienced hands exchange transfusion carries a very low operative risk. Nevertheless, infants who are initially very anaemic present a grave problem as this treatment is their only hope of survival. There are also other infants who appear well at the start of the transfusion, but become ill or die during the procedure.

Walker and Neligan (1955) discussed these problems and listed the probable factors involved as heart failure, shock and possibly biochemical changes. Campbell (1955) considered that deterioration during exchange transfusion was in many cases probably due to electrolyte disturbance, mainly hyperkalaemia. He noted, however, that in two infants having similarly high levels of serum potassium, one was ill and one quite well. Farquhar and Smith (1958) stated that 'changes in serum electrolytes were shared by infants who were disturbed and by those who showed no abnormality'. In a series of 18 consecutive cases of haemolytic disease studied in this hospital during 1958-59, serum electrolyte estimations and simultaneous electrocardiograph tracings were done at every 100 ml. during the exchange. There was no correlation between deterioration of the infant's condition observed clinically and the serum level of either calcium or potassium, and not a single electrocardiogram showed any evidence of electrolyte disturbance. Even when donor blood with a potassium level of 19·2 mEq/litre was used in one case there was no clinical distress, and the infant's serum potassium and electrocardiogram remained normal.

It has been my impression that with increasing experience and our present method of using packed donor cells, disturbances due to hyperkalaemia and hypocalcaemia play a decreasing role. I agree with O'Neill and Gordon (1959) that cardiac embarrassment is a more frequent cause of clinical distress. This may occur not only in infants who are already very anaemic and ill, but also during the exchange in an otherwise well baby. This paper attempts to assess the value of venous pressure measurements in the umbilical catheter during exchange transfusion and control of the speed of transfusion in relation to cardiac failure.

Criteria

The criteria for exchange transfusion were those recommended by Lathe, Claireaux and Norman (1958), the main factors being a cord haemoglobin below 15·5 g./100 ml. or a cord bilirubin of 5 mg./100 ml. or more, with a second exchange being indicated if the serum bilirubin reached 20 mg./100 ml. before the fifth day.

Method

The method employed was to measure in centimetres and record the height of the column of blood in the umbilical catheter, above the level of the sternal manubrium. Such measurements were made before the exchange transfusion, and during the procedure immediately after the injection of each 100 ml. of blood. The total time taken to complete the transfusion was noted, and a continuous record of the clinical status of the patient was made.

Material

The material upon which the recorded observations were made consisted of 15 consecutive exchange transfusions carried out as part of the routine work of the Paediatric Department during 1959-60. In addition there were three transfusions in which observations were recorded; they have not been included in this paper because of incomplete exchange transfusions (less than 60 ml. per lb. body weight) due to technical difficulties. Follow-up of these three infants over six months has shown them to be physically and mentally normal.

All the exchange transfusions were performed for the treatment of haemolytic disease of the newborn and none were carried out on premature babies without haemolytic disease. Three infants required two, and one infant three exchange transfusions; a single transfusion was sufficient in the other six babies.

Technique

The apparatus is that normally employed for exchange transfusion with one simple addition. The umbilical catheter used is made of 'portex'* tubing of 2·0 mm. bore, with a length of similar tubing joined to it at right angles

* Portex T Tubing manufactured by Portland Plastics, Hythe, Kent.

in an inverted T-shaped fashion (see Figure). The internal junction between the two arms of the T was made exact, with smooth even surfaces (to prevent blood clot forming). There was some initial difficulty about this detail, but the manufacturers overcame this.

The upright arm of the catheter is held perpendicular by threading a piece of silk through its upper open end, and looping this over a suitable support. The umbilical end of the catheter is then inserted into the umbilical vein. Blood is allowed to flow, or is withdrawn, as far as the T junction, when it enters the perpendicular arm. This should then be clamped with artery forceps at a distance of 20 or 30 cm. from the T junction (to avoid the area of venous pressure measurements) and further blood withdrawn into the syringe in the normal manner. When all the apparatus has been 'filled' with blood, the clamp may be removed. When the baby is at rest the height of the column of blood above the level of the sternal manubrium is measured (in centimetres) in the vertical arm of the catheter (umbilical venous pressure).

The apparatus is rinsed through with silicone solution before sterilization. Clotting in the vertical part of the catheter can be completely avoided by rinsing with sterile normal saline at every 100 ml. blood exchanged. This can easily be done without removing the catheter from the umbilical vein, by simply pinching it (between finger and thumb) on the umbilical side of the T junction, while rinsing is taking place. Heparin solution for rinsing is not necessary.

The horizontal limb of the catheter measures 60 cm., and the volume contained within this is 1·75 ml. As will be seen from the recorded data, the venous pressure recorded in the vertical limb of the catheter was most frequently 12 cm. or less. This means an increase in volume of the 'dead space' (extra to the usual form of apparatus) in the order of 0·35 ml. We do not consider this makes any significant difference to the efficiency of the exchange.

During treatment of the previously mentioned 19 cases in 1958-59, and in the early cases of this series of 10 cases, it was realized that most infants were without distress when the venous pressure measured no more than 12 cm. This figure was therefore accepted as the pressure at which blood may be injected without causing cardiac embarrassment. The upright limb of the T tube was therefore marked at a height of 12 cm. While injecting blood during the exchange this height was not exceeded, except when the baby cried or became restless; when this occurs it is wise to call a temporary halt. This technique was found to be a ready means of controlling the 'injection pressure' or speed of injection.

The minimum staff necessary for the procedure has been two doctors and one experienced nursing sister. With this degree of supervision no special snags have been encountered. The simple manipulations listed above may appear cumbersome when expressed on paper, but in practice are quite quickly carried out. They may also serve to keep the team 'on their toes' during what may (in a large baby) become a somewhat prolonged and tiring operation.

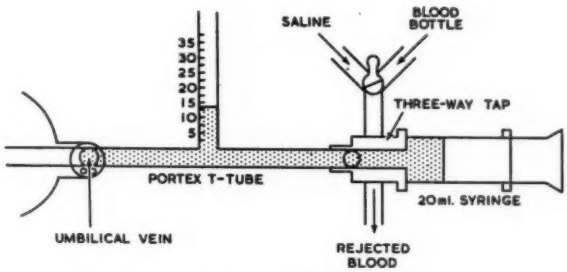

FIG. Exchange transfusion apparatus.

Results

At all times, except where expressly stated, the measurement of venous pressure in centimetres was recorded with the baby at rest. A 'glucose teat' was sometimes necessary as a 'comforter'.

Venous pressure before exchange varied from 3·5 to 19 cm. in the 10 infants. The maximum venous pressure recorded during transfusion was 25 cm.

The venous pressure at the conclusion of transfusion varied between 1·0 and 12 cm.

With the exception of Cases 2 and 6, which will be referred to later, all the infants were reasonably well clinically at the start of the procedure. The highest pre-transfusion venous pressure recorded in these eight children was 11 cm.

In the seven cases (nine exchange transfusions) who were well throughout the transfusion, all, except Case 5 (transfusion No. 8), had a maximum venous pressure of 12 cm. or less. In transfusion No. 8 one recording of 17 cm. was made, and all the others were between 10·5 and 12·5 cm.

In Case 2 (transfusion No. 3), weight 6 lb., serum bilirubin 18·2 mg. per 100 ml., the highest venous pressure before exchange was 19 cm. This infant was moderately cyanosed with increasingly laboured respiration: 20 ml. of blood were withdrawn at the beginning of the exchange, reducing the pressure to 3·2 cm., with marked clinical improvement and disappearance of cyanosis. During the exchange in this case the venous pressure rose to a maximum value of 25 cm.

In Case 7 (transfusion No. 10), weight 10 lb. 5 oz., cord bilirubin 5·0 mg. per 100 ml., the venous pressure before exchange was 3·5 cm. This infant was clinically very fit. It was decided to exchange at a speed which would previously have been regarded as safe (8·0 ml./minute), and it was noted that during injection the column of blood in the vertical arm of the T tube measured 36 cm. When injection was slowed down to what would have been regarded as very slow (5·0 ml./minute) the measurement was 19 cm.

TABLE

Case No.	Exchange Transfusion No.	Venous Pressure Before Exchange (cm.)	Maximum Venous Pressure During Exchange (cm.)	Venous Pressure End of Exchange (cm.)	Clinical State During Exchange	Follow-up
1	1	5·0	12·0	9·5	Satisfactory	
2	2	2·0	15·0	1·0	Very ill at start; oxygen required	
	3	19·0	25·0	6·5	Second exchange, ill at start, oxygen required	
3	4	5·5	5·5	1·0	Satisfactory	
	5	9·0	9·0	7·5	Satisfactory	All alive and mentally and physically normal
4	6	4·2	6·0	6·0	Good at start; oxygen needed at end	
5	7	1·0	6·5	2·0	Fair at start, mild cyanosis later; oxygen given	
	8	10·0	17·0	10·5	Excellent	
6	9	5·8	4·0	1·5	Ill, vomiting, suction required	
7	10	3·5	12·0	12·0	Satisfactory	
8	11	8·0	10·0	3·5	Occasional oxygen required	
	12	5·5	7·0	4·0	Satisfactory	
	13	11·0	10·0	5·5	Satisfactory	
9	14	2·5	5·0	5·0	Very well	
10	15	7·0	8·0	4·5	Very well	

Case 1 was also clinically fit, weight 6½ lb., cord haemoglobin 110% and bilirubin 6 mg. per 100 ml. An exchange of 80 ml./lb. was completed in 90 minutes, i.e. 5·8 ml. blood exchanged per minute. The venous pressure before exchange was 5 cm., the maximum 12 cm. and the final 9·5 cm.

Cases 2 and 6 were the most severely affected of the 10 infants, and were in the class referred to as 'pre-hydropic' by O'Neill and Gordon (1959).

In Case 6 (transfusion No. 9), weight 7 lb. 4½ oz., cord haemoglobin 36% and bilirubin 6·7 mg. per 100 ml., an 80 ml./lb. exchange was completed in 150 minutes, i.e. 3·8 ml. of blood exchanged per minute. The venous pressure before transfusion was 5·8 cm., maximum during the procedure was 4 cm., and the final pressure was 1·5 cm.

In Case 2 (transfusion No. 2) the infant was very ill and the cord blood figures of haemoglobin 27% and bilirubin 5·3 mg. per 100 ml., are the worst, in combination, that have been encountered so far in this hospital. A 60 ml./lb. exchange was completed in 105 minutes, i.e. 3·5 ml. blood exchanged per minute. It was considered imprudent to attempt an 80 ml./lb. exchange in this infant. Venous pressure before exchange was 2 cm., maximum 15 cm., and final 1·0 cm. The low initial figure is due to the fact that there had been blood loss after the cord was cut and this is therefore not a true pre-transfusion record. The results of the 10 cases are summarized in the Table.

Discussion

Although +4·0 cm. (Mollison, 1956) is regarded as the normal figure, in the cases under discussion there were no clinical signs of distress in those infants in whom the venous pressure measured 12 cm. or less. As illustrated in a well baby (Case 1) a resting venous pressure of this order will not be exceeded by a speed of exchange between 5 and 6 ml./minute. In Case 7 in which a speed of exchange up to 8 ml./min. was employed for a short period the recorded measurements confirm my previous impressions that a rapid injection of blood can elevate the venous pressure (during injection) to a dangerously high level. In an ill baby in whom the resting venous pressure is already high there would be the distinct possibility of cardiac embarrassment.

In Cases 2 and 6, because of their extremely precarious clinical condition, special precautions were taken to keep the 'injection pressure' below 12 cm. throughout the transfusion. This resulted in a very slow speed of injection of 3·5 to 4·0 ml./min., with obvious benefit to the infants, as the exchange transfusions were completed successfully, and in a six months' follow-up both infants remained physically and mentally normal.

At the completion of an exchange transfusion it is tempting in some cases to add a further 10 or 20 ml. of blood to finish with a higher haemoglobin level. In Case 7, although a well baby, an extra 10 ml. of blood injected at the conclusion of the exchange

raised the resting venous pressure from 7 to 12 cm. In an ill baby such a procedure could be disastrous. It is preferable to increase the haemoglobin by an extended slow transfusion of 20 to 30 ml. as a follow on (O'Neill and Gordon, 1959), or to give a small 'top-up' scalp vein transfusion at a later date.

A resting pressure lower than 4 cm. may indicate a seriously ill infant. This may arise if the venous pressure is high, for when the cord is cut, blood will immediately spurt out; if the umbilical vein has not been instantly catheterized the rapid loss of blood will have the effect of lowering the venous pressure before measurement has been possible. This happened in Case 2 (transfusion No. 2) where the venous pressure before transfusion was only 2·0 cm., and was undoubtedly a false reading. An initial venous pressure below 3·0 cm. may indicate a weak myocardium and should suggest caution.

Conclusion

Venous pressure was measured in the umbilical vein and recorded during exchange transfusion in 10 consecutive cases of haemolytic disease of the newborn.

In the eight infants who were clinically fair before transfusion the maximum venous pressure was 11 cm.

In those seven infants who remained without distress during the exchange transfusion the maximum venous pressure was about 12 cm.

With the use of a 'portex' T tube an 'injection pressure' of 12 cm. can be maintained throughout the procedure, thus limiting the speed of injection and avoiding cardiac overloading. The latter is the most frequent cause of distress, especially in the ill anaemic baby. The technique described is considered to be a useful method of treatment, especially in this type of patient.

It is with great pleasure that I record my thanks to Sister B. M. Barchard, Miss S. A. Broadley and Drs. T. Woodward, B. Weir and D. H. Livingston for their assistance with the transfusions and preparation of this paper, and also to Professor R. S. Illingworth and Dr. K. Holt for their helpful criticism.

References

Campbell, W. A. B. (1955). Potassium levels in exchange transfusion. *Arch. Dis. Childh.*, **30**, 513.

Farquhar, J. W. and Smith, H. (1958). Clinical and biochemical changes during exchange transfusion. *Ibid.*, **33**, 142.

Lathe, G. H., Claireaux, A. E. and Norman, A. P. (1958). *Recent Advances in Paediatrics*, ed. D. Gairdner, 2nd ed., p. 115. Churchill, London.

Mollison, P. L. (1956). *Blood Transfusion in Clinical Medicine*, 2nd ed., p. 502. Blackwell, Oxford.

O'Neill, E. M. and Gordon, R. R. (1959). Extended exchange transfusion in pre-hydropic infants. *Arch. Dis. Childh.*, **34**, 174.

Walker, W. and Neligan, G. A. (1955). Exchange transfusion in haemolytic disease of the newborn. *Brit. med. J.*, **1**, 681.

CONGENITAL ABNORMALITIES IN THE AFRICAN NEWBORN

BY

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As no figures were available on the incidence and type of congenital abnormalities in African peoples, 2,068 consecutive newborn babies were examined by us and the results are given in this paper. They were born between December 1956 and September 1957, in the maternity wards at Mulago Hospital, Kampala, in Uganda. This town has about 40,000 inhabitants. It is on the north shore of Lake Victoria, practically on the Equator and is 4,000 feet above sea level. Mulago Hospital is for Africans only and is the teaching hospital for medical students from the University College of East Africa (Makerere College).

Women are admitted for both normal and abnormal delivery. There is no domiciliary service, but two mission hospitals in the area also have maternity beds. The patients are drawn from many tribes, the Baganda forming the largest group. Antenatal clinics are held, but many of those who attend wait at home to see if natural delivery is possible. It is usual for women to wait until labour starts before coming to hospital. As there are few roads and travel during darkness is difficult, many patients are admitted in false labour. Patients live at varying distances from Kampala and five miles is thought to be near. A few patients are admitted from up-country centres. There are about 3,000 deliveries a year. It is from these patients that our material is taken.

Of the 2,068 babies, 141 were stillborn. It was not possible to do autopsies. It was difficult to see all the stillborn babies because relatives took the body away very soon after delivery. Of these stillborns, 40 were not seen by us, but it is reasonable to expect that any gross abnormality such as anencephaly would have been recorded in the notes. Major abnormalities are always recorded by the midwife or medical student delivering the mother. Two hydrocephalics (one with talipes) and one macerated foetus with syndactyly, brachydactyly and a funnel deformity of the chest were stillborn.

There were 52 twin births and two of triplets; all these babies were stillborn.

Table 1 shows the abnormalities found. The rate in this series is 5·4%. As Neel (1958) points out, any comparison of the frequency of congenital malformations in different series is handicapped by the fact that no two series are made up in the

TABLE 1

CONGENITAL ABNORMALITIES IN 2,068 AFRICAN NEWBORNS

Malformations	Number
1. Single malformations	
A. Musculo-skeletal system:	
Talipes equino varus	1
Bifid terminal phalanges of thumb	1
One phalanx each finger left hand	1
Polydactyly fingers	28
Genu recurvatum	3
B. Cardiovascular system:	
Congenital cyanotic heart disease type undetermined	1
C. Digestive system:	
Atresia ani	1
Harelip only	2
Harelip and cleft palate	1
Ileal atresia	1
Lymphangioma of tongue	1
D. Urogenital system:	
Hypospadias	3
Hydrocele of cord	1
E. Abnormalities of C.N.S.:	
Hydrocephalus	2
F. Organs of special sense:	
Ear malformation complex	2
Accessory auricles	5
Prehelicine fistulae	46
G. Integument:	
Ichthyosis	1
Hairy naevus	1
Cavernous naevus	1
Collodion skin	1
Accessory nipples	3
H. Syndromes:	
Mongolism	1
Gargoylism	1
2. Multiple malformations	
Macerated foetus with syndactyly, brachydactyly and funnel chest	2
Hydrocephalus and talipes equino varus	1
Total	112

Rate = 5·4% of births.

* Present address: The Hospital for Sick Children, Great Ormond Street, London W.C.1.

TABLE 2

EFFECT OF MATERNAL AGE ON MALFORMATIONS

	Age (years)						Totals
	0–19	20–24	25–29	30–34	35–39	40+	
Bantu	377	554	411	139	43	4	1,528
Non-Bantu	124	123	100	23	7	0	377
Insufficient information	—	—	—	—	—	—	163
Total	501	677	511	162	50	4	2,068
Bantu with malformations	16	24	26	8	3	0	77
Non-Bantu with malformations	9	4	4	0	1	0	18
Insufficient information, but with malformations	—	—	—	—	—	—	17
Total with malformations	25	28	30	8	4	0	112

$\chi^2 = 2{\cdot}4$ D. of F. = 3 $0{\cdot}5 > p > 0{\cdot}25$

TABLE 3

EFFECT OF BIRTH ORDER ON MALFORMATIONS

	1	2	3	4	5	6	7	8	9	10	Totals
Bantu	559	424	257	139	70	36	30	6	3	4	1,528
Non-Bantu	166	92	54	33	16	11	3	2	0	0	377
Insufficient information	—	—	—	—	—	—	—	—	—	—	163
Total	725	516	311	172	86	47	33	8	3	4	2,068
Bantu with malformations	31	25	18	7	3	2					86
Non-Bantu with malformations	12	4	3	1	1	1					22
Insufficient information, but with malformation	—	—	—	—	—	—					4
Total with malformation	43	29	21	8	4	3					112

$\chi^2 = 2{\cdot}32$ D. of F. = 4 $0{\cdot}75 > p > 0{\cdot}5$

same way. In some series many minor abnormalities are included and in others these are excluded. For example, McIntosh, Merritt, Richards, Samuels and Bellows (1954; booked hospital cases) find an incidence of 7·8% White and 6·3% non-White infants and they include many minor abnormalities. Other incidences which exclude many minor abnormalities are 1·47% (Carter, 1950; England, booked cases only), 1·63% (Coffey and Jessop, 1955; Ireland, hospital cases), 0·67% (Hegnauer, 1951; Germany, hospital cases), 1·11% (Nowak, 1950; Germany, hospital cases), and 1·02% (Neel, 1958; Japan, general population).

It is better to compare the incidence of particular abnormalities, but in a small series such as this comparison with other large series is not possible. Nevertheless, the incidence of many abnormalities is similar to that seen in Europe, harelip and cleft palate being an example. There are, however, some striking differences between the incidence of some malformations in Africans and in other parts of the world. For example, there were no babies with spina bifida or anencephaly and, moreover, analysis of the hospital records of 5,498 babies born between 1953 and 1955 showed only two cases of anencephaly and two of spina bifida. This low incidence of anencephaly has been noted before among native Africans in Johannesburg and Pretoria by Kahn (1956). In Britain, from three to 12 anencephalics and from three to eight cases of spina bifida would have been seen in 2,000 newborns. Geographical variation in the incidence of anencephaly is discussed in detail by Penrose (1957). He points out that though there is a great variation of frequency of occurrence in different parts of Europe, the incidence is, on the whole, greater among Europeans than among Asians or Africans.

Polydactyly is very common, the incidence being 1·4%. The extra digit is attached in all cases to the proximal phalanx of the little finger, commonly

TABLE 4

MEAN BIRTH ORDER BY MATERNAL AGE AND MALFORMATION

	Mean Birth Order	Mean Maternal Age in Years
All babies	2·34	24·2
Those with malformations	2·17	24·63
Those with prehelicine fistulae	2·33	24·87
Those with extra digits	2·00	23·63
Those with malformations other than prehelicine fistulae or extra digits	2·09	25·23

TABLE 5

DISTRIBUTION OF MALFORMATIONS AMONG BANTU AND NON-BANTU

(Malformation rates/1,000 births in brackets)

	All Ethnic Groups	Bantu	Non-Bantu	Insufficient Information
Number of babies examined	2,068	1,528	377	163
All malformations	112 (54·2)	87 (56·9)	25 (66·3)	—
Prehelicine fistulae	46 (22·2)	40 (26·2)	6 (15·9)	—
Extra digits	27 (13·1)	18 (11·8)	9 (23·9)	—
Malformations other than prehelicine fistulae and extra digits	39 (18·9)	29 (19)	10 (26·5)	—

by skin alone. It is rudimentary, usually made up of one phalanx and sometimes has a nail. In 11 cases the abnormality was unilateral and in 16 bilateral. Two other babies had a similar condition of the toes and one of these had an accessory digit on the little finger of the same side. Both Bantu and non-Bantu were affected, the incidence being insignificantly higher in the non-Bantu. Accessory digits are uncommon in the United Kingdom. Marshall (1959) examined 1,000 consecutive European babies born at Queen Charlotte's Hospital on this point. None had accessory digits.

Prehelicine fistulae were more common, the incidence being 2·2%. With this condition the incidence is higher in the Bantu, but the difference is not significant ($\chi^2 = 2{\cdot}9$; D. of F. = 1). Of Marshall's 1,000 cases referred to above, only two had prehelicine fistulae (0·2%).

Detailed information on the effect of maternal age and birth order is given in Tables 2, 3 and 4. No significant effect is seen. Table 5 shows the distribution of malformations among Bantu and non-Bantu.

Discussion

As Neel (1958) and others have noted, the total incidence of congenital malformations is comparable in different races. There are, however, striking differences in the incidences of particular malformations. This first series of newborn babies from Africa confirms these observations. Although it was not possible to assess the degree to which our findings were influenced by the admission of obstetric emergencies the total incidence of congenital abnormalities is similar to that of other races. There are significantly fewer severe abnormalities of the central nervous system such as spina bifida and anencephaly. The two cases of hydrocephalus seen were not associated with spina bifida of which there were no examples. There were many more examples of polydactyly and prehelicine fistulae than are seen elsewhere. At first sight it may appear that there is a smaller incidence of congenital heart disease. The figures for this are not accurate, however, since the babies usually stayed in hospital for one to three days only and a follow-up examination was not practicable.

Summary

The first series describing congenital abnormalities in African newborn babies is presented.

The total incidence of malformed children is 5·4%; this is similar to the rate for other races. There are, however, striking differences in the incidence of particular malformations.

Very few severe abnormalities of the central nervous system such as anencephaly, spina bifida and hydrocephalus are encountered.

There are many more examples of polydactyly and prehelicine fistulae than are seen elsewhere.

Thanks are due to Professor Coralie Rendle-Short of the Department of Obstetrics and Gynaecology at Makerere College, Kampala, for allowing us access to her patients and for her encouragement, and to the Chief Medical Officer, Uganda, for permission to publish. We also gratefully acknowledge much valuable help and criticism from Dr. Cedric Carter of the Medical Research Council's Genetics Unit at The Hospital for Sick Children, Great Ormond Street, London.

REFERENCES

Carter, C. O. (1950). Maternal states in relation to congenital malformations. *J. Obstet. Gynaec. Brit. Emp.*, **57**, 897.

Coffey, V. P. and Jessop, W. J. E. (1955). Congenital abnormalities. *Irish J. med. Sci.*, 30.

Hegnauer, H. (1951). Missbildungshäufigkeit und Gebäralter. *Geburtsh. u. Frauenheilk.*, **11**, 777.

Kahn, E. (1956). Personal communication, quoted by Penrose (1957).

Marshall, W. C. (1959). Personal communication.

McIntosh, R., Merritt, K. K., Richards, M. R., Samuels, M. H. and Bellows, M. T. (1954). The incidence of congenital malformations: a study of 5,964 pregnancies. *Pediatrics*, **14**, 505.

Neel, J. V. (1958). A study of major congenital defects in Japanese infants. *Amer. J. hum. Genet.*, **10**, 398.

Nowak, J. (1950). Häufigkeit der Missgeburten in den Nachkriegsjahren, 1945-49. *Zbl. Gynäk.*, **72**, 1313.

Penrose, L. S. (1957). Genetics of anencephaly. *J. ment. Defic. Res.*, **1**, 1.

DELAYED VISUAL MATURATION

BY

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In view of the fact that there may be delay in maturation in any of several fields of development (Illingworth, 1961) it would not be surprising if some children showed delay in visual maturation. Having studied the visual development in two such children I searched the literature for information on the matter. The search included all volumes of the Quarterly Cumulative Index Medicus and standard textbooks on ophthalmology. I found very few references to the subject.

Doyne (1930), writing from his experience at The Hospital for Sick Children, Great Ormond Street, London, wrote that 'In some cases the development of sight is only delayed'. He described a child of 3 months of age who showed no sign of vision. Ophthalmoscopic examination showed pigmentary deficiency of the retina and choroid. Sight began to develop from the seventh month, and was normal by 18 months. He referred to the frequency with which mentally subnormal children showed no apparent evidence of vision for some months, and wrote that the commonest cause of delayed sight development was albinism.

Doggart (1957) mentioned the problem of infants who showed no sign of vision in the early weeks, and who subsequently saw normally. He suggested that this might be due to delayed myelination of the optic nerve, described by several French authors as 'La pseudoatrophie grise du nerf optique'. Doggart also referred to the frequency with which optic atrophy and other lesions were wrongly diagnosed. He wrote: 'For every genuine abnormality that escapes detection, at least a dozen imaginary ones are described'.

Duke-Elder (1949) described visual agnosia as the 'inability to recognize or orientate objects perceived, although the reception of their sensory impressions is intact'. He felt that though cases of visual agnosia are seen, the condition is not well recognized.

My colleague, Mr. A. B. Nutt (1960), also referred to the frequency with which fundus changes were suspected in infants referred because of apparently defective vision. He mentioned the fact that the optic disc was paler than that of older children, and that some degree of retinal hypoplasia was normal, so that the macula had a stippled appearance. He wrote that the assessment of sight of an infant did not depend on the appearance of the disc, but on the correlation of the child's visual behaviour with his behaviour in other fields of development.

Law (1961) wrote at length on the problem of the visually defective infant, on the basis of material at the Moorfields Hospital, London. I am indebted to him for allowing me to see the script of the paper before publication. He referred to the difficulty in determining whether a pale optic disc in an infant was normal or abnormal, and emphasized the need for caution in diagnosing optic atrophy in infants. He thought that 80% of infants suspected of having defective vision would prove to have normal or near normal sight, but the evidence for this view was not strong. He described 28 infants referred on account of defective vision. Ten of them, all thought in infancy to have pale optic discs, proved to have normal or almost normal vision. They were followed up for periods ranging from two months to nine years. The others were not adequately followed up, or had gross optic atrophy on examination. Law referred to the frequent finding of mottling of the macula, and of the 'pepper and salt' appearance of parts of the fundus. He rightly referred to the importance of relating the infant's visual perception to the level of mental development. Unfortunately it is not possible to determine from Law's paper the age at which the children began to see or respond to what they saw.

Sorsby and Williams (1960) described blindness in infants with normal eyes or minimal fundus anomalies. The anomalies included the diffuse fine pigmentation called the 'pepper and salt' fundus. They described two families in which children showing these changes developed progressive blindness. The need for caution in interpreting these

minimal changes is obvious in the light of the papers by Law and Sorsby and Williams.

I have not found other papers relevant to the subject, either in French or Italian, nor other papers on blindness in infants without ophthalmoscopic signs; neither have I found a description of cases similar to those below. I have, however, discussed the problem with many paediatric colleagues, and most of them have seen one or two infants presenting features similar to those described.

Below are the case reports of two children seen by me at the Children's Hospital, Sheffield.

Case Reports

Case 1. I saw this boy at the age of 3½ months, through the courtesy of Dr. S. Yudkin of London. He had been born two weeks prematurely, weighing 5 lb. 8 oz. (2,500 g.), after a normal pregnancy and labour, and a normal delivery. There had been no significant infection in pregnancy; and he was well in the newborn period. There were no siblings. There was no family history of delayed development or of other relevant abnormalities.

His parents, who were both intelligent, complained that he could not see. They said that he took no notice of anything, did not focus his eyes and did not smile at them, and that he did not watch them as they talked to him. He had, however, begun turning his head to sound at 12 weeks, which is the average age for this 'milestone', and he had been vocalizing from the age of 7 weeks, which is again average. He was said to smile at nothing in particular when lying in his cot.

On examination his appearance was normal and he was vocalizing normally. The head circumference was average for a small baby—15¾ in. His weight was 12 lb. 7 oz. In the prone position he bore the weight on the forearms, with his chest well off the couch, and when he was pulled from the supine to the sitting position, there was only minimal head lag. He bore good weight on the legs. The hands were open, and the knee, ankle jerks and muscle tone were normal. He held a rattle placed in the hand and played for a long time with it. In motor and manipulative development he was entirely average, and the vocalizations, though difficult to assess, appeared to be normal. The urine did not contain phenylpyruvic acid.

He appeared to take no notice of his surroundings. He did not watch his mother or father. He did not follow the dangling ring. He took no notice of bright objects, such as a metal hammer. I thought that he appeared to see light, when using the method described by André Thomas and Saint-Anne Dargassies (1952), and the pupils reacted to light. There was no nystagmus and ophthalmoscopic examination was entirely normal. My colleagues, Mr. G. Mackie, and Mr. A. B. Nutt, agreed with these findings.

The baby showed the picture of developmental dissociation (Illingworth, 1958). The diagnosis made was delayed visual maturation, and I told the parents that although it was impossible to be sure, I thought that the outlook was good and that he would see normally in time, and that mental development was normal.

He began to show signs of seeing at the age of 5 months, and at the age of 6 months I saw him laughing. He lifted his head from the supine spontaneously (an achievement typical of a 6-month-old baby). He was now following a light, dangling ring or bell, but not as far as an average 6-month-old baby. He followed objects in the lateral and vertical direction, but not for 180°. He repeatedly opened his mouth when the feeding bottle approached his lips. Motor development was normal. He transferred objects from hand to hand.

At 10 months he weighed 22 lb. The head circumference was 17½ in. He made immediate attempts to pick up the Gesell 8 mm. pellet, but could not quite achieve finger-thumb apposition. There was almost an index finger approach to objects. The grasp of one-inch cubes was mature. Vocalizations were good. He bore full weight on the legs, but would not stand holding on to furniture. He was sitting securely, and had begun to sit without support at 7 months. He actively banged and rang the bell. He repeatedly opened his mouth on the approach of a piece of chocolate. He was not able to wave bye-bye or play pat-a-cake.

The boy was normal in his behaviour; in some aspects of development his developmental level was that of a 9-month-old baby, but he was quite up to the average in motor development. His visual pursuit and visual development were normal.

Case 2. This girl, whom I have described in part elsewhere (Illingworth, 1960) was a full-term baby born normally after a normal pregnancy. She was well in the newborn period. At the age of 3 days she first showed the signs of spasmus nutans. I have not heard of this condition in a child so young.

For the first six months she showed no evidence of vision. She did not smile. Her mother, an intelligent woman, was convinced that she was blind. Her family doctor and a doctor at the infant welfare clinic concurred. At 4 months she took no notice of bright Christmas-tree lights, but she was able at that age to hold and play with a rattle placed in the hand, and she had been turning her head to sound from the age of 3 months. At 5 months she was taken to Mr. Muirhead, ophthalmological surgeon at Chesterfield, to be certified as blind. He declined to certify this, though agreeing that she showed no sign of vision. The pupil reactions, optic discs and fundi were normal. At this age she took no notice of the feeding bottle when it was approaching her, and showed no response until it touched her lips. She began vocalizing 'mama'.

At the age of 6 months she first began to smile at her mother and to follow with her eyes. She now began to reach for objects and get them. The spasmus nutans persisted. At 8 months she was able to sit without support, at 9 months to play pat-a-cake, and at 10 months to wave bye-bye, handle a toy and part with it, and to cast objects on to the floor—all average for the age.

At 11 months she held her arms out for clothes,

which is average for the age. At 16 months she was speaking in sentences, and I was impressed with her advanced speech, her interest in surroundings, and her alertness. She had begun to acquire sphincter control. She was somewhat hypotonic in the lower limbs and did not walk without support until she was 2 years old. I regarded this as isolated delay in motor development, and of no significance. She showed spasmus nutans, with the characteristic lateral movements of the head, brought on by concentration on an object, and the usual peculiar way of looking at objects out of the eye corners. Her eyesight and fundi were normal. At 33 months she was speaking in long sentences, she was able to put on her pants, skirt, cardigan, shoes and socks, and sometimes to fasten buttons. On the picture card she named eight objects (Gesell; average for 36 months), and with the uncoloured geometric forms (Gesell) she achieved the level of a child of 45 months. She did not co-operate in drawing nor in repeating digits. There were slight residual signs of spasmus nutans. It was obvious that she was a bright normal child with normal vision and a better than average level of intelligence.

Discussion

When a child is referred for an opinion because he or she does not appear to see, by far the commonest finding is mental subnormality, as indicated by retardation in other aspects of development. A full developmental examination is therefore necessary. Even if the child is retarded in other fields of development, examination of the eyes and the optic fundus is essential, for optic atrophy, cataract and other eye defects are commonly associated with mental subnormality. If, however, the child who appears not to see at the appropriate age, is found to have developed normally in other respects, and no defect is found in the eye, the likely diagnosis would be blindness or delayed visual maturation. The possibility that the child will see normally in time is an important one to remember, because one has to discuss the prognosis with the parents.

The same applies to the retarded child who does not seem to respond to what he sees. If examination of the eye does not reveal any abnormality, the odds are that the child will see normally when he is older. The difficulty which commonly arises, however, is interpretation of the pale optic disc, which may or may not be normal. If there is doubt about such a disc, the odds are that the child will see normally in time.

I am frequently asked to see babies because of suspected blindness, and the great majority are found to be mentally subnormal. I often feel that they are relatively more retarded in visual recognition than in other fields—an example of what I have termed developmental dissociation (Illingworth, 1958), and it may well be that delayed visual maturation is more common in retarded children than in others, just as generalized delay in maturation is more common in mentally subnormal ones than in children who will prove to have a normal level of intelligence (Illingworth, 1961).

An important feature of children with delayed visual maturation may well be the absence of roving nystagmus. It is difficult to say how soon roving nystagmus is seen in blind children, but it is certainly seen by the age of 3 or 4 months.

When faced with an otherwise normal infant who fails to show visual response, there is a remote possibility of autism. Such a child may fail to smile at his mother or to show interest in his surroundings.

It is not possible to say whether the child with delayed visual maturation is unable to see, or is able to see but unable to interpret what he sees (visual agnosia).

The condition of delayed visual maturation in an otherwise normal child is uncommon, but it is clear from discussion with other paediatricians and with ophthalmologists that it is not very rare. It will probably always be impossible to give an accurate prognosis to anxious parents, because it may well be that there are many gradations between blindness which will be permanent and 'blindness' which will be temporary, as in the two children described. Prognosis, therefore, must always be guarded, but it is a great help to parents if reasonable hope of complete normality can be given.

Neither of these children has yet been followed into school life and there is always the possibility that perceptual difficulties will reveal themselves in later years.

I am indebted to Dr. S. Yudkin of London and Dr. B. Graham of Sheffield for referring one of these children to me, and to Mr. E. G. Mackie, F.R.C.S., and Mr. A. B. Nutt, F.R.C.S., for their ophthalmological findings. I am indebted to Mr. H. C. Muirhead, F.R.C.S., of Chesterfield, for his ophthalmological findings in the second case, and to Dr. Margaret Eastwood for referring the girl to me.

References

Doggart, J. H. (1957). Infantile fundus lesions in relation to mental capacity. *Brit. med. J.*, **2**, 933.
Doyne, P. G. (1930). Amaurosis in infants. *Practitioner*, **125**, 174.
Duke-Elder, W. S. (1949). *Textbook of Ophthalmology*, vol. 4. Kimpton, London.
Illingworth, R. S. (1958). Dissociation as a guide to developmental assessment. *Arch. Dis. Childh.*, **33**, 118.
—— (1960). *The Development of the Infant and Young Child, Normal and Abnormal.* Livingstone, Edinburgh.
—— (1961). *J. Pediat.* (in the press).
Law, F. (1961). The problem of the visually defective infant. *Trans. ophthal. Soc.*, **80**, 3.
Nutt, A. B. (1960). Ophthalmic manifestations in paediatric practice. *Ibid.*, **79**, 315.
Sorsby, A. and Williams, C. E. (1960). Retinal aplasia as a clinical entity. *Brit. med. J.*, **1**, 294.
Thomas, A. and Saint-Anne Dargassies, S. (1952). *Etudes neurologiques sur le Nouveau-né et le jeune Nourrisson.* Masson, Paris.

CONGENITAL ABNORMALITIES OF THE FEMUR

BY

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From the Royal College of Surgeons

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Congenital defects of the femur vary from simple hypoplasia of the bone to complete absence. Classification of these defects has been suggested by Nilsonne (1928) and by Mouchet and Ibos (1928), but neither has met with general acceptance. In more recent years Golding (1939, 1948) has demonstrated the close association of the short femur with congenital coxa vara, and has emphasized that these are variations of the same underlying abnormality. The clinical distinction between the various types of femoral defect is important as a guide to the prognosis of limb development.

From an examination of patients with congenital abnormalities of the femur the following classification is suggested:

1. Simple femoral hypoplasia.
2. Congenital coxa vara.
3. Femoral hypoplasia with coxa vara.
4. Pseudarthrosis of the femur.
5. Hypoplasia of the lower femoral epiphysis.
6. Complete absence of the femur.

Although these patients commonly have other skeletal defects, the major congenital abnormalities affecting the nervous system, or in the chest and abdomen, appear to be rare. Their span of life is thus rarely affected, and detailed autopsy or pathological examination of the limb is rarely possible. From the clinical examination of these patients, however, and from serial radiographs, much information can be obtained about the clinical course of the limb abnormality, and the nature of the underlying disturbance of growth.

Clinical Material

The records of the Royal National Orthopaedic Hospital and The Hospital for Sick Children for the past 10 years have been examined, and patients with this diagnosis have recently been reviewed. With the addition of one case from Guy's Hospital, 38 examples of this defect have been collected, 19 of these have been reported in detail elsewhere (Ring, 1959) under the title of simple femoral hypoplasia, and will only be considered briefly. A true indication of its incidence is difficult to obtain, but it appears to be the commonest congenital defect causing major abnormalities of limb growth.

Clinical Features

There is no evidence that this is a familial disorder, and careful inquiry of the parents has revealed no evidence of other congenital disorders within the immediate family. The history of the pregnancy and delivery has failed to indicate any significant infection or abnormality at this time. In most patients the abnormality is apparent at birth, but where the inequality of leg length is slight, the diagnosis may not be made until the child begins to walk. To ordinary clinical testing the abnormality is confined to the skeleton; there is no evidence of an associated muscular or nervous abnormality, although in the presence of gross defects muscle attachments may be bizarre. Occasionally there is also a partial or complete absence of the fibula, usually with an associated foot defect. In the present series this has always involved the same side as the femoral defect.

Simple Femoral Hypoplasia (19 cases). The affected thigh is shorter than its fellow, but may appear more bulky. It is often bowed laterally, and the patella is high and small. The leg is held in external rotation, and the hip cannot be rotated internally beyond the neutral position. Radiographs of the femur show no abnormality apart from the shortening, but there is usually some thickening of the cortex of the femur at the centre, and a small beak on its outer side. The radiographs often resemble those of a healed birth fracture, and many of these cases were initially regarded in this light. The distinction is an important one since the congenital short femur always grows less rapidly than its fellow, and the inequality of leg length therefore tends to progress. In this group the definitive shortening does not usually exceed three inches and may well be less.

FIG. 1.—Congenital coxa vara showing deformity of the head and neck and elevation of greater trochanter.

These cases have already been considered in detail elsewhere (Ring, 1959).

Congenital Coxa Vara (three cases). Abnormalities in the hips of these patients are rarely detected before they start to walk, although limitation of abduction, and a very slight shortening of the limb, if the lesion is unilateral, are apparent at birth. Where both hips are affected there is a waddling gait, and a pronounced lumbar lordosis. Both abduction and internal rotation of the hip are limited, but the head of the femur can usually be felt in the acetabulum.

In the early radiographs ossification of the head of the femur is usually delayed. The varus deformity of the femoral neck may be apparent soon after birth, but more commonly develops during the second year of life. Ossification defects in the lower part of the femoral neck are common, but not invariable. In this small group mineralization of the head and neck has proceeded relatively normally (Fig. 1). The length of the femur is probably affected mainly by the deformity of the upper end, and the shortening of the limb rarely exceeds one inch (Table). Indeed, true growth in length of the femur, from trochanter to femoral condyles, often appears unaffected.

Femoral Hypoplasia with Coxa Vara (five cases). This type of defect combines the features of the first two groups. The shortening of the limb is usually noticed at birth, or during the early months of life. There is an asymmetry of the thigh creases, and the leg is held in external rotation (Fig. 2). Internal rotation of the hip is absent, and abduction limited. The greater trochanter is elevated, but there is no

TABLE

Case No.	Age (years)	Shortening (in.)	Treatment	Associated Defects
*Congenital short femur:**				
1	2½	1	None	—
2†	7	None	Bilateral osteotomy	—
3	15	1½	None	—
Femoral hypoplasia with coxa vara:				
4	10	4	Stapled	None
5	5	4 (femur) 2 (tibia)	Extension prosthesis	Absent fibula
6	7	2	None	Scoliosis with congenital abnormalities
7	16	Unknown	Amputation through knee	Premature fusion head of femur
8	12	5	Extension prosthesis	None
Pseudarthrosis of the femur:				
9	20	7¾	Patten	None
10	4	7½	Symes' amputation	Partial absence of fibula
11	6	Unknown	Arthrodesis of knee; Symes' amputation	None
12	2	5	None	None
13	6	Unknown	None	None
14	½	3	Bone grafting	None
Hypoplasia of the lower femoral epiphysis:				
15	4	2	None	Genu valgum
Complete absence of femur:				
16	5	None	Bilateral prosthesis	Talipes; absent fibula; congenital amputation of arms
Bilateral short femur:				
17	3	Unknown	Prosthesis	Absent fibula
18	10	5	High boot	Fixed flexion hip and knee
19	7	2½	Caliper	Genu valgum

* Excluding simple femoral hypoplasia. † Bilateral.

FIG. 2.—Congenital short femur and coxa vara. There is external rotation of the limb, the thigh is short and bowed.

FIG. 3.—Coxa vara and short femur. The secondary centre for the head of the femur has not yet appeared.

FIG. 4.—Gross shortening of the right thigh associated with congenital pseudarthrosis of the femur.

evidence of hip instability and the head of the femur can usually be palpated within the acetabulum.

Radiographs of the legs show that the affected femur is short, and bowed laterally, within an area of cortical sclerosis on the outer side. The upper end is expanded, the metaphysis is broad, and the epiphyseal centre for the head is late in appearing (Fig. 3). The acetabulum is often shallow. Careful examination of the relationship of the upper end of the femur to the acetabulum permits the diagnosis of coxa vara and short femur to be made before the upper bony epiphysis has appeared. The presence of this centre makes the diagnosis more certain, and reveals the definitive shape of the femur. Defects of this type may be associated with congenital abnormalities of the other femur, of a greater or lesser extent.

In this type of deformity growth of the limb is profoundly depressed, and shortening varies between three inches and six inches at maturity. Even in the absence of gross congenital abnormalities of the tibia or fibula, the growth of the leg below the knee is usually depressed. An indication of this can often be obtained from the early radiographs which show delay in the appearance of the upper epiphyseal centre of the tibia.

Congenital Pseudarthrosis of the Femur (six cases). This term has been used to describe the grosser type of femoral shaft defect. The child presents at birth with a very short thigh, although the development of muscle is often apparently normal (Fig. 4). There is usually a flexion deformity of the hip, and abduction is limited or absent. There is commonly an associated congenital defect of the leg or foot.

The early radiographs show a short and narrow femoral shaft, with delay in appearance of the upper and lower femoral epiphyses. In this condition the centre for the lower end usually develops during the first year, although it may show abnormalities of shape, usually associated with a genu valgum. As the child grows the femur increases in length, but its upper end attains a level above the acetabulum, indicating a progressive coxa vara. The centre for the head of the femur is almost always present, and remains within the acetabulum (Fig. 5).

FIG. 5.

FIG. 5.—Radiograph of congenital pseudarthrosis of the femur. The shaft of the femur is displaced upwards, but the head remains in the acetabulum.

FIG. 6.—Congenital pseudarthrosis of the femur before exploration showing the shaft of the femur opposite the acetabulum.

FIG. 6.

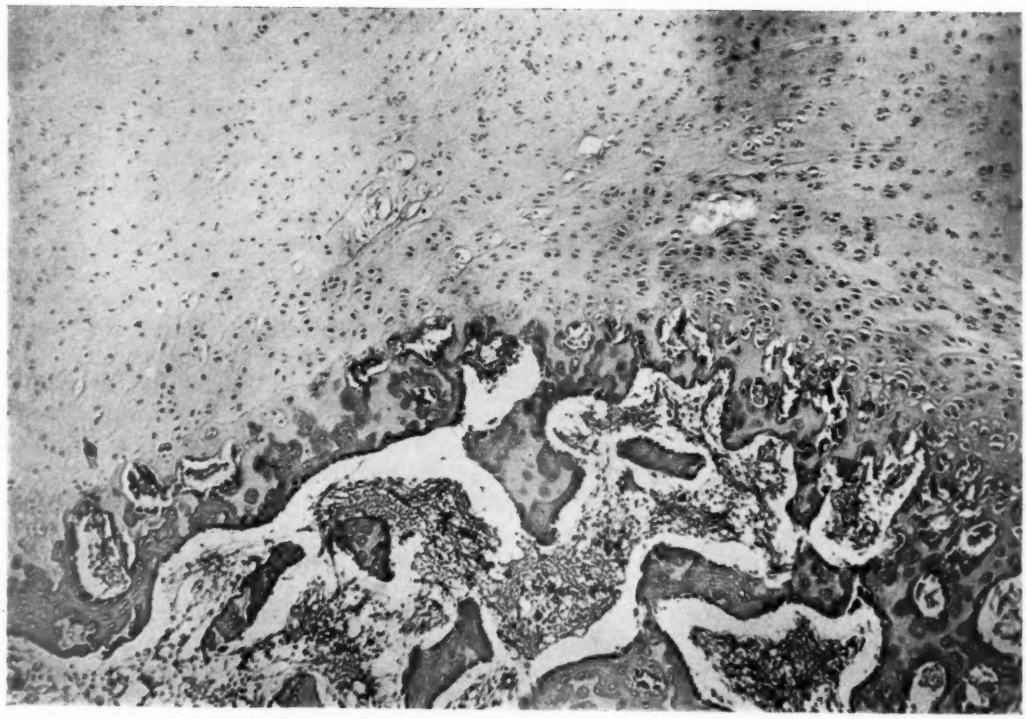

FIG. 7.—(The lower part of the figure contains the end of the marrow cavity and 'metaphysis'.) There is a suggestion of columnar arrangement above the cartilage cells and this appears to be a slowly ossifying area.

FIG. 8.—Radiographs taken three months after the operation showing the child in Fig. 6. The fibular graft can be seen extending into the head of the femur which has now ossified. There is a large bar of new bone formation between the upper end of the femur and the side wall of the pelvis.

Thus, although the shaft of the femur appears to be dislocated in relation to the hip joint, there is no true instability, and the head of the femur and the shaft remain in continuity, but not by bone. The upper end of the shaft of the femur is often capped in the older child by a small plate of bone, which probably represents the centre of ossification for the greater trochanter.

Shortening in these patients is due to a combination of coxa vara and a growth defect. By controlling the varus deformity it might be possible to diminish the progress of limb inequality. One child was subjected to operative exploration (Fig. 6). The upper end of the femur was found to be complete in its cartilaginous form, and no true pseudarthrosis was present. The upper part of the metaphysis ended by splaying into the cartilage of the femoral neck, and sections of this region showed the normal process of endochondral ossification (Fig. 7). The cartilage of the upper femur was divided and a wedge removed to abduct the shaft of the femur, and a fibular graft driven across from the upper part of the femur into the cartilaginous head. After this operation the head of the femur rapidly ossified, although para-articular ossification still limited hip movement (Fig. 8).

Hypoplasia of the Lower Femoral Epiphysis (one case). Most congenital defects of the femur affect the upper end either predominantly or completely, although the delay in the appearance of the secondary centre for the lower end indicates that the disturbance of growth may affect the whole bone. In association with defects of the upper part of the femur abnormalities in shape of the lower femoral epiphysis may also appear, and may contribute to the development of a genu valgum (Fig. 9). Complete absence of the lower femoral epiphysis has been seen in one patient. The condition affected both legs, but there was none of the other stigmata of the congenital short femur. It is more likely that this type of abnormality is related to the multiple congenital abnormalities of the epiphyses, rather than the short femur.

Complete Absence of the Femur (one case). This type of defect is usually detected at birth and is commonly bilateral. The thigh is short, and the femur cannot be palpated. The buttocks are broad, and the musculature of the gluteal region is well developed. There are usually associated deformities of the limb below the knee, and deformities of the upper limb may also be present (Fig. 10).

FIG. 9.—The lower femoral epiphysis which is malformed, with a genu varum deformity. The femur is also bowed and short.

Although walking may be a little delayed, even in the presence of a bilateral defect, mobility is quite good, although instability is marked. The radiographs of the limb show that the femur is completely absent, but the tibia fails to articulate with the pelvis by some distance. As the child grows a small ossicle representing the lower end of the femur may appear in the radiographs, emphasizing how resistant the lower end of the bone is to this deformity.

Bilateral Defects (three added cases). There are five patients in this series with a deformity of both femurs. In two of them, one with coxa vara, and one with complete absence of the femur, the defect was symmetrical. In the other three patients there was a profound inequality of limb length. The association of two different types of femoral defect in the same patient confirms the view that these defects are all variants of a common abnormality (Fig. 11).

FIG. 10.—Congenital absence of both femora and of the right forearm with talipes.

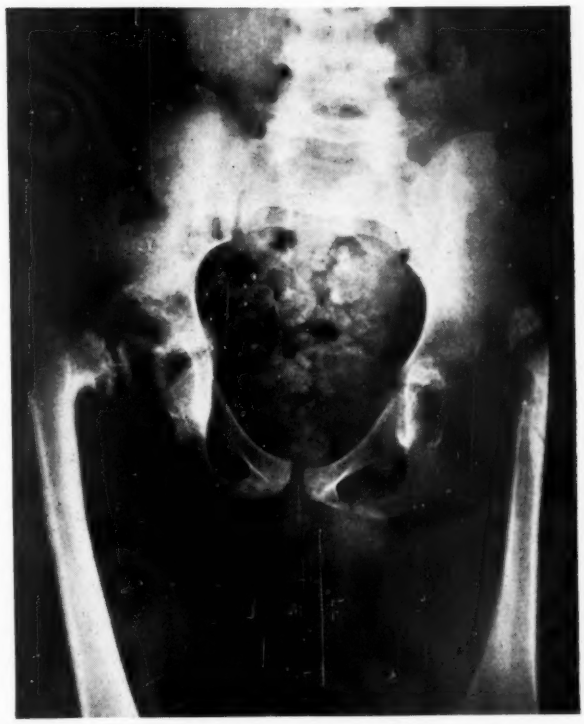

FIG. 11.—Bilateral short femur. On the right is a gross coxa vara, on the left a pseudarthrosis. The head of the femur on the left is just visible in the acetabulum.

Discussion

Aetiology. Careful inquiry into the family history of these patients, into the history of the pregnancy and that of the birth has failed to find any evidence of a familial factor in this disorder. There is clearly a close association between other congenital defects of the skeleton, and particularly with congenital absence of the fibula. Occasionally both femora are affected. In the simple coxa vara, however, the defects are usually symmetrical, but in the other type of disturbance the femora tend to be unequally affected. The significance of this observation may not be great, since symmetrical disturbance of femoral growth might well pass unnoticed.

In all congenital defects of the femur there is a tendency for the upper metaphysis to be the most severely affected part of the bone. From the study of the serial radiographs in these children it appears that the primary defect lies in the cartilaginous primordium of the femur. It is suggested that the abnormality of structure of this tissue is such that in the minor aberrations it is resistant only to the process of endochondral ossification. Such a resistance accounts for the delay in the appearance of secondary centres of ossification and also for the broad area of weakness in the upper end of the bone. Under the stress of weight-bearing, or possibly of simple muscle activity, the relationship between the head of the femur and the neck becomes disturbed. The development of coxa vara is thus dependent upon a change in the resistance of the cartilage to stress, whilst the failure of growth lies in a resistance to the normal process of endochondral ossification. In the simple coxa vara resistance to ossification is minimal, and shortening is slight, but in the more severe types of deformity changes in the upper end of the femur, and shortening are closely allied.

The association of the congenital short femur with other types of congenital abnormalities of the skeleton is more in favour of a primary disturbance of the cartilaginous framework than a vascular defect, or an intrauterine fracture. It must be conceded, however, that there is no reason why the upper metaphysis of the femur is so commonly involved in this type of abnormality.

Prognosis. The disability in congenital defects of the femur is largely related to the extent of the inequality of limb length. Fixed flexion in the region of the hip joint, although it increases the apparent shortening of the limb, rarely occasions any other disturbance. The externally rotated position of the limb does not give rise to any functional disability, and there is no evidence that it encourages degenerative changes in the hip.

In the individual child, the outlook depends primarily upon the extent of the femoral defect. The shortening of the limb may be predicted with fair accuracy at any age by relating the length of the two femora. Thus in a child with a femur only half as long as the normal one, the shortening in an adult will be somewhere between seven and nine inches. In the presence of coxa vara without other evidence of the congenital short femur shortening is usually insignificant, and in a simple femoral hypoplasia will probably not exceed three inches. Where the two defects are combined the inequality may be as much as six inches and this will be exceeded in the presence of congenital pseudarthrosis of the femur.

Treatment. The presence of fixed deformity of the hip requires treatment in patients with minor femoral defects to permit a normal gait. In the presence of severe defects it may occasionally be necessary to permit a prosthesis to be fitted. Coxa vara without shortening may require subtrochanteric femoral osteotomy, and the results of this operation are usually good (Le Mesurier, 1948).

Relatively few of the children in this series have been subjected to treatment for the limb inequality. Many of them, of course, have not yet reached the age at which definitive treatment is possible. Where the shortening amounts to three inches or less, it is clearly amenable to treatment by stapling the knee epiphyses of the longer limb, or by femoral shortening. The number of patients treated in this way is too few to indicate the value of each of these procedures.

The more severe disturbances of growth have been treated by the provision of suitable appliances. In the presence of a well-developed muscular system, these patients manage to carry a high boot or a shoe with a patten with ease. The function of children in the extension prosthesis is excellent, but the foot tends to be forced into an uncorrectable equinus, thus prejudicing any later attempt to reduce limb inequality. This appliance is also unsightly in the older patient, and some of these children have been treated by Syme's amputation at an early stage, thus permitting a less obtrusive limb to be worn. The advantages of this procedure must be weighed against the reluctance of the patient and the parents to sacrifice a normal foot.

In the fitting of an artificial limb in the older patient a knee flexion piece is rarely possible. For this type of patient van Nes (1950) has described a rotation-plasty which may well be of value. By fusing the knee and rotating the leg through 180°

the ankle is available to activate the knee-flexion part of the prosthesis.

Summary

A classification of congenital defects of the femur has been presented, and eight examples of this defect have been grouped.

The clinical and radiological picture in these patients, and the growth of the short limb has been described.

The nature of the growth disturbance in these patients has been discussed.

I am most grateful to Mr. J. S. Batchelor, Sir Denis Browne, Professor J. I. P. James, Mr. G. C. Lloyd-Roberts, Mr. K. I. Nissen and Mr. David Trevor who have permitted me to examine and report upon patients under their care.

References

Golding, F. C. (1939). Congenital coxa vara and the short femur. *Proc. roy. Soc. Med.*, **32**, 641.
—— (1948). Congenital coxa vara. *J. Bone Jt Surg.*, **30B**, 161.
Le Mesurier, A. B. (1948). Developmental coxa vara. *Ibid.*, **30B**, 595.
Mouchet, A. and Ibos, P. (1928). Considérations sur l'absence congénitale du fémur. *Rev. Orthopéd.*, **15**, 117.
van Nes, C. P. (1950). Rotation-plasty for congenital defects of the femur. *J. Bone Jt Surg.*, **32B**, 12.
Nilsonne, H. (1928). Über den kongenitalen Femurdefekt. *Archiv. orthop. Unfall-Chir.*, **26**, 138.
Ring, P. A. (1959). Congenital short femur. Simple femoral hypoplasia. *J. Bone Jt Surg.*, **41B**, 73.

HYDRAMNIOS IN RELATION TO FOETAL MORTALITY

BY

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It has long been recognized that hydramnios is associated with a high foetal mortality and a high incidence of foetal abnormalities.

In this paper the incidence of foetal mortality and morbidity associated with hydramnios has been calculated and an attempt has been made to show the prognosis for the foetus of a mother with hydramnios.

Material

A retrospective survey was made of patients at the Jessop Hospital for Women, Sheffield, from 1949 to 1958 inclusive. This hospital admits primigravidae and women with complications of pregnancy.

In the 10-year period there were 16,214 pregnancies resulting in 16,628 births. In the same period there were 256 pregnancies with hydramnios, resulting in 287 births (Table 1). In the 15,853 live births the incidence of hydramnios was 18 per 1,000, compared with an incidence of 3·1 per 1,000 given by Malpas (1937) in Liverpool, and Prindle, Ingalls and Kirkwood (1955) in Boston. Moya, Apgar, James and Berrien (1960) found 79 infants associated with hydramnios in 24,316 deliveries, an incidence of 3·2 per 1,000 births.

Method

In formulating criteria for the diagnosis of hydramnios we have accepted conditions similar to those of Scott and Wilson (1957), i.e. either the recording of clinical hydramnios by two independent obstetricians, or the recovery of 1,500 ml. or more of liquor at amniotomy.

Maternal and infant records and autopsies were examined.

Results

Of the 287 infants in this series, 43% were stillbirths or died in the neonatal period; 164 babies survived beyond the neonatal period (Table 1). Prindle *et al.* (1955) found a perinatal mortality of 51% in 155 infants, and Moya *et al.* (1960) reported a mortality of 29% in 79 infants associated with maternal hydramnios.

One hundred and eighteen infants (41%) had one or more congenital defects. The abnormalities found are grouped into systems in Table 2. Of the central nervous system the following abnormalities were found: anencephaly in 59 (three in one of twins), hydrocephaly, encephalocele, meningocele, or iniencephaly in 14, mongolism in one, congenital bulbar palsy in one, palatal paralysis in one, and one mentally retarded child. Achondroplasia occurred in five, Klippel-Feil syndrome in one, mediastinal obstruction due to hamartoma of the lung in one, congenital heart disease in two, congenital goitre in one and choanal atresia in one. In the gastro-intestinal tract there was absence of the mandible in one patient, cleft palate and harelip in eight,

TABLE 1

SURVIVAL—MORTALITY FIGURES, AND PERCENTAGE DISTRIBUTION OF STILLBIRTHS AND NEONATAL DEATHS

	Hospital Population: 16,628	Hydramnios Series: 287
Stillbirths	775 (5)	89 (31)
Neonatal deaths ..	477 (3)	34 (12)
Total deaths	1,252 (8)	123 (43)
Survivals	15,376 (92)	164 (57)

Figures in parenthesis are percentages.

TABLE 2

DISTRIBUTION OF CONGENITAL ABNORMALITIES IN 118 OUT OF 287 INFANTS ASSOCIATED WITH HYDRAMNIOS

Distribution of Congenital Abnormality	Total	Alive	Dead
Central nervous system	75	3	72
Musculo-skeletal system.. ..	6	—	6
Ear, nose and throat	1	1	—
Respiratory system	1	—	1
Cardio-vascular system	2	1	1
Gastro-intestinal system ..	31	7	24
Miscellaneous	2	2	—

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oesophageal atresia in seven, duodenal atresia in one, diaphragmatic hernia or defects in four, severe hydrops in six, foetal ascites in one, and imperforate anus in two.

Other causes of death were: cerebral haemorrhage (10), intrauterine and intrapartum anoxia (six), prematurity (five), respiratory distress syndrome (two), infections (two) and atelectasis (two).

In the 10-year period there were 10 babies with oesophageal atresia, of whom seven were associated with maternal hydramnios. In this series one in every 41 cases of hydramnios was associated with oesophageal atresia. Carvalho (1954) estimated that in one out of 12 cases hydramnios was due to oesophageal atresia. Prindle *et al.* (1955) found that 20 out of 107 babies with this condition were associated with maternal hydramnios, and Scott and Wilson (1957) found hydramnios in 12 out of 13 cases of oesophageal atresia. Of our seven patients with oesophageal atresia, six were stillborn or died in the neonatal period.

In this study, achondroplasia was found in six infants out of 16,628 births, of which five were associated with hydramnios. There were no survivors.

Discussion

These results confirm the view that hydramnios is associated with gross abnormalities in the foetus, and a high morbidity and mortality rate.

Little is known of the cause and origin of hydramnios. In many of the congenital abnormalities a mechanical factor may be involved, preventing normal swallowing of amniotic fluid by the foetus *in utero*, as suggested by Scott and Wilson (1957). This is not, however, a relevant consideration in achondroplasia, and the reason for the association is not clear.

Summary

A retrospective study of 287 births associated with hydramnios revealed that 43% of the babies were stillborn or died in the neonatal period. Congenital abnormalities were present in 41% of infants.

I wish to thank Professor R. S. Illingworth for encouragement in writing this paper and Dr. N. F. Coghill for constructive criticism.

References

Carvalho, O. (1954). Hidrâmnio e atresia esofagica congênita. *Ann. bras. Gynec.*, **38**, 137.

Malpas, P. (1937). The incidence of human malformations and the significance of changes in the maternal environment in their causation. *J. Obstet. Gynaec. Brit. Emp.*, **44**, 434.

Moya, F., Apgar, V., James, L. S. and Berrien, C. (1960). Hydramnios and congenital anomalies. *J. Amer. med. Ass.*, **173**, 1552.

Prindle, R. A., Ingalls, T. H. and Kirkwood, S. B. (1955). Maternal hydramnios and congenital anomalies of the central nervous system. *New Engl. J. Med.*, **252**, 555.

Scott, J. S. and Wilson, J. K. (1957). Hydramnios as an early sign of oesophageal atresia. *Lancet*, **2**, 569.

CLEFT LIP AND PALATE: SEASONAL INCIDENCE, BIRTH WEIGHT, BIRTH RANK, SEX, SITE, ASSOCIATED MALFORMATIONS AND PARENTAL AGE

A STATISTICAL SURVEY

BY

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Cleft palate, with or without cleft lip, is one of the more common congenital malformations in man. Two recent English surveys have reported a birth incidence of about one in 600 (MacMahon and McKeown, 1953; Pleydell, 1960) and this conforms well to careful surveys carried out in other countries of Europe (Fogh-Andersen, 1942) and the U.S.A. (Ivy, 1957).

For the past 10 years it has been the practice of the Plastic Surgery Unit at the Churchill Hospital to record in cases of this malformation, information regarding birth weight, date of birth, age of parents and birth rank. The site of the cleft (left, right or central) was always noted and in most cases the presence of any additional congenital malformations. In all, data are available in 456 cases, though the full information is not given in every instance.

The present paper deals with an analysis of these data in an attempt to throw light on possible aetiological mechanisms of this deformity. Group I refers to cases of isolated harelip, Group II to isolated cleft palate and Group III to combined harelip with cleft palate (Davis and Ritchie, 1922).

The Present Inquiry

Edwards (1958a) and Record and Edwards (1958) have detected a strong seasonal trend in the incidence of anencephaly and congenital dislocation of the hip respectively. Thus it seemed worthwhile to analyse the present data, especially as Edwards (1961) has noted a seasonal tend in cases of Group I cleft lip, and our analysis is by the method described in his paper (Table 1). Birth weight, birth rank, sex incidence, site of cleft and associated abnormalities are shown in Tables 2-6.

The control series for parental age (Table 7) was obtained in the following way. Parental age was recorded in 1,026 consecutive births at University College Hospital from March 1956 to October 1957. A regression was established for father's age on mother's age for each birth rank separately and for the total material. These data could not be used as a control series because of the different age and birth rank distribution of hospital, as opposed to domiciliary, deliveries.

However, using the material in the Registrar-General's report (1954) for maternal age, the expected paternal age could be calculated, using the regressions established as above.

Discussion

The pathogenesis of these malformations is controlled not by any single factor, but by a number of factors both hereditary and environmental, and by interactions between them. Furthermore, the members of a surgical series, as presented here, have only one feature in common—the nature of the lesion to be repaired—and otherwise represent a heterogeneous collection of different entities. Data of this nature cannot differentiate between the roles of heredity and environment in the causation of this condition, still less define clearly any aetiological factors. It can, however, provide pointers in this direction.

Seasonal Incidence. It has been shown by these results (Table 1) that seasonal influences appear to play no significant part in the causation of these malformations. This is in contrast to the findings of Edwards (1961).

Birth Weight. Birth weights are on the whole

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TABLE 1
SEASONAL INCIDENCE

Cleft Group	Birth Month												χ^2	Significance
	1	2	3	4	5	6	7	8	9	10	11	12		
I	4	10	3	11	10	5	10	5	9	7	7	8	1·56	0·5> p >0·3
II	19	14	21	18	19	18	14	11	16	23	9	13	1·91	0·5> p >0·3
III	14	6	16	8	17	10	11	16	7	13	16	16	1·63	0·5> p >0·3
Total cases	37	30	40	37	46	33	35	32	32	43	32	37	0·41	0·9> p >0·8

TABLE 2
BIRTH WEIGHT

Cleft Group	Sex	Totals	Mean Birth Weight of Clefts	S.D.	Mean Birth Weights of Controls	Significance
I	M	53	7·61	0·14	7·61	p >0·10
	F	26	7·31	0·25	7·31	p >0·10
II	M	69	7·63	0·15	7·61	p >0·10
	F	83	7·03	0·12	7·31	0·02> p>0·01
III	M	96	7·45	0·14	7·61	p >0·10
	F	46	7·13	0·20	7·31	p >0·10

Controls from Birmingham series of McKeown and Gibson (1951) and MacMahon and McKeown (1953) corrected for parity.

TABLE 3
BIRTH RANK

Cleft Group	Position in Family									χ^2	Significance
	1	2	3	4	5	6	7	8	9		
I	35	21	14	8	4	1	0	1	2	0·56	0·5> p >0·3
II	74	54	22	7	7	4	3	3	2	0·05	0·9> p >0·8
III	51	42	25	14	6	4	1	0	0	0·16	0·7> p >0·5
Total cases ..	160	117	61	29	17	9	4	4	4	0·53	0·5> p >0·3

The statistical analysis is by the method of Edwards (1958b). The control series is from figures for the whole country published by the Registrar-General for 1954, this being the median birth year of the present series.

low (Table 2). This is not unexpected with a severe congenital malformation and it is interesting that in Group I this decrease is least. It is most marked in Group II females and this conforms to the findings of Lutz (1959).

Birth Rank. The birth rank distribution (Table 3) is not significantly different from normal. However, if it is analysed by the sex of the patient, we find a marked primiparity effect in Group I females.

	Group I (cleft lip only)								
Birth Rank ..	1	2	3	4	5	6	7	8	9
Females ..	16	5	2	4	1	0	0	1	1
Males	19	16	12	4	3	1	0	0	1

This effect is not repeated in any other group. (Normal ratio for birth rank 1 to birth rank 2 = 1·32. In Group II males it is 1·25 and in females 1·48, and in Group III males 1·04, females 1·50.)

Incidence, Sex and Site. It has been argued that Groups I and III form one sub-division of this malformation and Group II another. The main argument in favour of this hypothesis has been the similar excess of affected males in Groups I and III (about 2:1 in most series) as opposed to equality or even a slight excess of females in Group II. The present data support this hypothesis (Tables 4 and 5). The possible reasons for the male excess in Groups I and III will be discussed later. The incidence by site conforms well to the data of Fogh-Andersen. No explanation can be given at the moment for the preference of this lesion for the left side. The incidence on the various groups con-

TABLE 4
INCIDENCE AND SEX

Cleft Group	Total	% of Series	Males	Females	Males (%)
I	93	20·4	61	32	65·6
II	211	46·3	94	117	44·5
III	152	33·3	103	49	67·8
Totals ..	456	—	258	198	56·5

TABLE 5
SITE OF CLEFT

Cleft Group	Right	Left	Bilateral
I	27 (29·0%)	48 (51·6%)	18 (19·4%)
II	Central		
III	31 (20·4%)	82 (53·9%)	39 (25·7%)

TABLE 6
ASSOCIATED ABNORMALITIES

Cleft Group	Nos.	Abnormality
I	1	Syndactyly
II	19	Pierre Robin's syndrome (retrognathism)
	4	Klippel Feil's syndrome
	2	Mucous fistulae of lower lip and syndactyly
	1	Treacher Collins' syndrome
	1	Ectrodactyly
	1	Talipes
III	1	Hypospadias
	1	Micrognathia
	1	Polydactyly

forms well to the Birmingham birth data (MacMahon and McKeown 1953), but not to the operative series of Fogh-Andersen who found about 50% of Group III, and roughly equal incidence of Groups I and II. The reason for this discrepancy is not clear.

Associated Malformations. This is an operative and not a birth series. The incidence of congenital malformations (Table 6) would be expected to be lower, therefore, than in the series of MacMahon and McKeown (1953) since all gross malformations would have been excluded by early death. Group II, however, is very interesting from this point of view since isolated cleft palate seems to occur with remarkable frequency as a constituent of syndromes which are inherited in a dominant manner such as those of Pierre Robin and Treacher Collins and ectrodactyly. In addition, a father and son are included with the syndrome of cleft palate with mucous fistulae of the lower lip (Calnan, 1952; Van der Woude, 1954). In our family syndactyly was also present.

The syndrome of Pierre Robin is, however, numerically by far the most important. In the past such children tended to die soon after birth due to the tongue falling back causing asphyxia; they are now surviving with better nursing care, and the condition of the lower jaw improves with age. This syndrome is inherited in an irregularly dominant manner and the gene concerned may account for quite a large proportion of Group II cases. An analysis of parental age was made separately for these complex syndromes and for simple Group II cases, but revealed no differences which could not be attributed to chance.

Parental Age. MacMahon and McKeown (1953) showed that maternal age but not birth rank was raised in Groups I and III but not Group II. We were unable to confirm this for Group I, but found a marked increase in Group III (Table 7). A smaller increase in Group II could well have been due to chance. Furthermore, our data suggest that the more important factor in the raised parental age was the *paternal* and not the maternal age. In an attempt to explain the puzzling asymmetrical distribution of the lesion and the difference in sex incidence an analysis of variance was performed to determine whether this raised paternal age in Group III could be correlated with patients of a particular sex or with a particular site of lesion.

TABLE 7
PARENTAL AGE

Cleft Group	Totals	Father		Mother	
		Mean Age	S.D.	Mean Age	S.D.
I	83	31·4	6·48	28·3	5·81
II	163	32·9	8·43	29·0	5·85
III	136	33·9	7·78	29·3	6·05
Controls		31·6 (var. = 0·14)		28·3	

Comparison with controls:

Group		Significance
I	Fathers	$p > 0·1$
	Mothers	$p > 0·1$
II	Fathers	$0·1 > p > 0·05$
	Mothers	$p > 0·1$
III	Fathers	$0·01 > p > 0·002$
	Mothers	$0·1 > p > 0·05$

Group III	Males	Females	
Right	23	8	$\chi^2 = 1·39$
Left	43	26	
Bilateral ..	23	13	$p = 0·5$

Analysis of variance (paternal age) is as follows:

	Degrees of Freedom	Sum of Squares	Mean Square	Significance
Between sexes ..	1	72	72	$p>0{\cdot}2$
Between sites ..	2	28	14	$p>0{\cdot}2$
Interactions ..	2	41	20·5	
Residual	130	8,692	66·86	

This analysis does not show any differences in paternal age by sex or site which are unlikely to be due to chance. However, the age of fathers of female patients is higher than that of males.

Patients	Mean Age of Father	Mean Age of Mother
47 females	34·6	29·7
89 males	33·1	29·1

Such large differences were not seen in Groups I and II.

Group	Patients	Mean Age of Father	Mean Age of Mother
I	28 females ..	31·5	28·5
	55 males ..	31·0	28·0
II	87 females ..	32·5	28·7
	76 males ..	33·4	29·3

An examination of parental age by birth rank was also made. The full results are not reproduced here, but the following table gives the ages of the parents of first births.

Group	Patients	Mean Age of Father	Mean Age of Mother
I	19 males ..	28·1	25·6
	14 females ..	30·4	27·6
II	30 males ..	30·1	26·6
	37 females ..	28·6	26·0
III	29 males ..	31·9	28·1
	18 females ..	31·8	26·9
Controls		28·5	25·3

This suggests an excess of elderly primiparae among the parents of female Group I children and among the parents of male Group III children.

Conclusions

An attempt has been made to provide pointers to the elucidation of the aetiology of this complex of congenital malformations. The excess of males in Groups I and III suggests that females are less susceptible to the interactions of polyfactorial genetical and environmental factors which are concerned in the pathogenesis of this sub-division. Thus, there is evidence that advanced maternal age at first birth may predispose to a Group I malformation in females and to a more severe Group III malformation in males. In the same way other less potent factors may cause a cleft lip in males, with a lower threshold of resistance, but nothing at all in females.

The increased paternal age, in Group III especially, suggests (Penrose, 1955) that fresh paternal mutations are concerned in the pathogenesis of this condition. Such mutations might be especially important in the fathers of female patients, who are older, since it has been argued above that females may have a higher threshold of resistance to environmental and genetical factors responsible for these malformations.

There is suggestive evidence, both because of the very different sex ratio in Group II and because of the incidence of isolated cleft palate as a constituent of various complex syndromes thought to be inherited in a dominant manner, that single genes may play a large part against a background of polyfactorial genes and environmental factors in the determination of this condition. The moderately raised parental age, once again more marked for fathers than mothers, suggests that fresh mutations may play a role. Such fresh mutations both in this Group and in Group III compensate for genes lost due to early death, as in Pierre Robin's syndrome.

We wish to thank the various surgeons concerned for permission to examine records of their cases and one of us (J.S.C.) wishes to thank Dr. A. C. Stevenson for kindly providing accommodation in the Population Genetics Research Unit, and the University of Oxford for a generous research grant during this study. We wish to thank Dr. J. H. Edwards for advice on treatment of these data and for allowing us to see a manuscript before publication.

References

Calnan, J. (1952). Congenital double lip: record of a case with a note on the embryology. *Brit. J. plast. Surg.*, **5**, 197.

Davis, J. S. and Ritchie, H. P. (1922). Classification of congenital clefts of the lip and palate. *J. Amer. med. Ass.*, **79**, 1323.

Edwards, J. H. (1958a). Congenital malformations of the central nervous system in Scotland. *Brit. J. prev. soc. Med.*, **12**, 115.

—— (1958b). A note on the interpretation of $n \times 2$ tables. *Ibid.*, **12**, 141.

—— (1961). The recognition and estimation of cyclic trends. *Ann. hum. Genet.*, **25**, 83.

Fogh-Andersen, P. (1942). Inheritance of harelip and cleft palate. *Op. dom. Biol. hered. hum., Kbh.*, Vol. 4.

Ivy, R. H. (1957). Congenital anomalies as recorded on birth certificates in the Division of Vital Statistics of the Pennsylvania Department of Health for the period 1951-55 inclusive. *Plast. reconstr. Surg.*, **20**, 400.

Lutz, K. R. (1959). Birth weights in cleft palate. *Cleft Palate Bull.*, **9**, 47.

McKeown, T. and Gibson, J. R. (1951). Observations on all births (23,970) in Birmingham, 1947; II: Birth weight. *Brit. J. prev. soc. Med.*, **5**, 98.

MacMahon, B. and McKeown, T. (1953). The incidence of harelip and cleft palate related to birth rank and maternal age. *Amer. J. hum. Genet.*, **5**, 176.

Penrose, L. S. (1955). Parental age and mutation. *Lancet*, **2**, 312.

Pleydell, M. J. (1960). Anencephaly and other congenital abnormalities. An epidemiological study in Northamptonshire. *Brit. med. J.*, **1**, 309.

Record, R. G. and Edwards, J. H. (1958). Environmental influences related to the aetiology of congenital dislocation of the hip. *Brit. J. prev. soc. Med.*, **12**, 8.

Van der Woude, A. (1954). Fistula labii inferioris congenita and its association with cleft lip and palate. *Amer. J. hum. Genet.*, **6**, 244.

LEUKAEMIC MENINGITIS

BY

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Patients with leukaemia now live longer and have greater opportunity to develop complications both due to therapy and to the disease itself. The treatment of leukaemic infiltration of the meninges has received little attention in this country, possibly because it has been regarded as a terminal event in a fatal disease. This is not necessarily true. Intracranial complications of acute leukaemia are seen in children in haematological remission who are otherwise well. We report here the case of a boy who had two episodes of raised intracranial pressure due to leukaemic infiltration whilst in clinical and haematological remission.

Case Report

A boy of 4¾ years attended St. Thomas' Hospital because of bone pains, bruising and pallor. He was found to have a blast cell leukaemia with a haemoglobin of 5·8 g. per 100 ml., white cells 20,000 per c.mm. (87% blast cells) and platelets 35,000 per c.mm. He was transfused with fresh blood and given prednisone (15 mg., t.d.s.) together with 6-mercaptopurine (50 mg., b.d.). His white cell count fell rapidly to 200 per c.mm., but after two weeks his haemoglobin had risen spontaneously and he appeared to be in remission. The dose of prednisone was gradually reduced over the next two months, but maintenance therapy with 6-mercaptopurine (10 mg., b.d.) was continued.

He was seen at weekly intervals, maintained on 6-mercaptopurine (10 mg., b.d.) and remained in complete haematological and clinical remission until nine months after the start of the illness when he began to have recurrent headaches which lasted for one hour or more, often associated with nausea. In addition he complained of 'seeing double'. Apart from these transient episodes he was well and refused to stay away from school. He was found to have bilateral papilloedema, but no other neurological abnormalities were detected. He was afebrile. The blood pressure was 110/80 mm. Hg, the liver and spleen were not palpable, there was no bruising and no lymphadenopathy. Haematological studies showed haemoglobin 12·4 g. per 100 ml., white cells 5,800 per c.mm. (with no abnormal cells) and platelets 173,000 per c.mm. His bone marrow contained 10% blast cells, but was otherwise normal.

Lumbar puncture was performed cautiously under general anaesthesia and produced an opalescent fluid under increased pressure (over 300 cm. C.S.F.). The cerebrospinal fluid contained 914 cells per c.mm., mainly leukoblasts, protein 50 mg. per 100 ml. and glucose 50 mg. %. No organisms were seen. He was treated with three intrathecal injections of 5 mg. 'amethopterin' (methotrexate) at intervals of three days and the cells in the cerebrospinal fluid fell to 90 per c.mm., most of which were lymphocytes. Despite this, the cerebrospinal fluid pressure remained over 300 c.mm. Whilst in hospital his headaches ceased and his disc margins became more distinct. A further lumbar puncture one week after the end of treatment showed only 5 cells per c.mm. all of which were lymphocytes. His ocular fundi were almost normal and he was free from symptoms. His blood picture was unaffected by the intrathecal therapy.

For three months after this episode he was clinically and haematologically normal and was maintained on 6-mercaptopurine (10 mg., b.d.). He then had two severe headaches, one of which was associated with vomiting. No abnormal signs were detected and on this occasion his ocular fundi were thought to be normal. From the haematological standpoint his remission continued. Haemoglobin 12·9 g. per 100 ml., white cells 6,300 per c.mm. and platelets 365,000 per c.mm. The bone marrow now appeared normal with no excess of blast cells, yet again the cerebrospinal fluid was under increased pressure and contained 372 cells per c.mm. with protein 35 mg. per 100 ml. He was treated with 5 mg. methotrexate intrathecally on three occasions at intervals of three days. There were no further symptoms and when the cerebrospinal fluid was examined four weeks later there were only 10 cells present. He remains well.

Comment

Intracranial leukaemic infiltration is often found at autopsy. Leidler and Russell (1945) found it in 83% of a series of 31 cases, yet clinical evidence of involvement of the central nervous system is less commonly noted. It was present in only 20% of the 334 cases studied by Schwab and Weiss (1935). Since the use of more effective chemotherapy, cases of children receiving such treatment who have developed signs of intracranial involvement are being reported (Poncher, Waisman, Richmond, Horak

and Limarzi, 1952; Sansone, 1954; Sullivan, 1957; Meneely, 1958; Whiteside, Philips, Dargeon and Burchenal, 1958; Cramblett, 1959; Murphy, 1959). Hamilton and Elion (1954) showed that the concentration of labelled 6-mercaptopurine in cerebral tissue was only one-tenth of that found in blood and that an even greater differential existed between its concentration in blood and cerebrospinal fluid. It appears likely that antimetabolites cross the blood-brain barrier poorly and that normally effective blood concentrations are unable to inhibit the production of abnormal cells protected within the cerebrospinal axis. It is presumably for this reason that, as in the patient reported here, active intracranial leukaemic proliferation may occur in the absence of clinical, peripheral blood or bone marrow relapse. This finding has two important implications. It suggests that continuous treatment with an antimetabolite inhibits the leukaemic process in the bone marrow and is largely responsible for the maintenance of clinical remission. Secondly, it suggests that autochthonous proliferation of leukaemic cells may take place *in situ* in the central nervous system and that their presence is not due to infiltration of primitive cells released from the bone marrow.

Intracranial leukaemia may affect either the meninges or the brain itself. In the latter case the child may present with weakness of the extremities and the cerebrospinal fluid usually contains less than 500 cells. Here the response to treatment is less favourable. If, however, the meninges are mainly involved the symptoms are headache, irritability, vomiting and disturbances of vision. The child is found to have papilloedema and there may be radiological evidence of raised intracranial pressure. The cerebrospinal fluid contains an excess of leukoblasts, usually more than 1,000 per c.mm. It is in cases of this predominantly meningeal type that intrathecal methotrexate has been most effective (Murphy, 1959). Methotrexate (0·5 mg. per kg.) is given intrathecally every third to fifth day until the cell count in the cerebrospinal fluid returns to normal. This treatment, which is remarkably non-toxic, is preferable to radiotherapy in that symptoms are more rapidly controlled and there is no likelihood of alopecia.

Since the treatment with intrathecal methotrexate is both simple and effective, it is important to realize that 'leukaemic meningitis' may occur in a child in complete remission. The signs and symptoms of meningeal involvement may, as in the case reported here, be minimal; so headache or any unexplained change of temperament in a child being treated for leukaemia is therefore an indication for a diagnostic lumbar puncture.

We are most grateful to Dr. Ruth Porter of Lederle Laboratories for her prompt help in arranging supplies of intrathecal methotrexate.

References

Cramblett, H. G. (1959). Recognition and treatment of intracranial manifestations of leukemia. *A.M.A. J. Dis. Child.*, **97**, 805.

Hamilton, L. and Elion, G. B. (1954). The fate of 6-mercaptopurine in man. *Ann. N.Y. Acad. Sci.*, **60**, 304.

Leidler, F. and Russell, W. O. (1945). The brain in leukemia. A clinicopathologic study of twenty cases with a review of the literature. *Arch. Path. (Chicago)*, **40**, 14.

Meneely, A. W. (1958). Leukaemia in children—Ten year survey. *Med. Bull. Harrisburg Polyclin. Hosp.*, **2**, 3.

Murphy, M. Lois (1959). Leukemia and lymphoma in children. *Pediat. Clin. N. Amer.*, **6**, 611.

Poncher, H. G., Waisman, H. A., Richmond, J. B., Horak, O. A. and Limarzi, L. R. (1952). Treatment of acute leukemia in children with and without folic acid antagonists. *J. Pediat.*, **41**, 377.

Sansone, G. (1954). Pathomorphosis of acute infantile leukaemia treated with modern therapeutic agents; 'meningoleukaemia' and Frölich's obesity. *Ann. paediat. (Basel)*, **183**, 33.

Schwab, R. S. and Weiss, S. (1935). The neurologic aspect of leukemia. *Amer. J. med. Sci.*, **189**, 766.

Sullivan, M. P. (1957). Intracranial complications of leukemia in children. *Pediatrics*, **20**, 757.

Whiteside, J. A., Philips, F. S., Dargeon, H. W. and Burchenal, J. H. (1958). Intrathecal amethopterin in neurological manifestations of leukemia. *A.M.A. Arch. intern. Med.*, **101**, 279.

LIPODYSTROPHIC MUSCULAR HYPERTROPHY

BY

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A bizarre disorder was recently encountered in a female child. There was severe lipodystrophy affecting the entire body, generalized muscular hypertrophy, large hands and feet, a markedly protuberant abdomen, hepatomegaly with biochemical and histological evidence of liver dysfunction, a large clitoris, enlarged cystic ovaries and a low fasting blood sugar concentration. This entity is not unique; patients with identical or similar features have previously been described under a variety of titles including the beguiling one of 'leprechaunism' (Ziegler, 1928; Hall, Sunderman and Gittings, 1936; Hansen and McQuarrie, 1940; Lawrence, 1946; Corner, 1952; Murray, 1952; Donohue and Uchida, 1954; Tizard, 1954; Berardinelli, 1954; Fontan, Verger, Couteau and Pery, 1956; Schwartz, Schafer and Renold, 1960; Seip, 1959) (see Table).

It is intended to detail the clinical and other findings in this unusual case and to suggest that the syndrome results from excessive secretion of a specific pituitary hormone.

Case Report

The patient, A.J., was first seen at the age of 2 years and 10 months. Pregnancy had been uneventful, delivery normal and the birth weight was 6 lb. 12 oz. Her appearance at birth was described as 'peculiar' in that she was thin and bony, lacked subcutaneous fat and had a wrinkled face. She gained weight 'but never filled out'. At the age of 6 months enlargement of the clitoris was noticed. At about the same time diarrhoea first appeared, the stools being green, loose and offensive and containing mucus but not blood. Protuberance of the abdomen had been apparent from a very early age and at about 1 year enlargement of the feet was noticed. She sat at 9 months, crawled at 1 year and walked at 18 months. Her speech was limited to a few words. The father was 32 and the mother 20 years old and they were not related. The patient was born of the second pregnancy, the first resulting in a stillborn child of normal appearance. There was a normal female sibling of 18 months.

On physical examination (Figs. 1-3) the length was 95 cm. (90%), span 94 cm., and weight 15 kg. (75%). Subcutaneous fat was lacking over the entire body. There was marked generalized hypertrophy of muscles, especially in the scapular region and extremities and muscle power was extremely good. There was a light brown pigmentation of the skin, particularly over the exposed areas and a fine growth of hair on the face, trunk and limbs; scalp hair was abundant, curly and reddish brown. The head was of normal shape with a circumference of 47·5 cm. A paucity of facial fat gave her an older appearance and made the nose and ears seem unduly prominent. There were 18 teeth, pointed and widely spaced. The thyroid gland was not palpable. A grade 1 parasternal blowing systolic murmur was present and the blood pressure was 80/50 mm. Hg. The abdomen was markedly protuberant and the umbilicus everted. A smooth liver edge was palpated 5 cm. below the right mid-costal margin. The enlarged clitoris was almost 2 cm. long. There was no pubic hair and the vaginal introitus was normal. The superficial veins of the extremities were very prominent, probably as a result of the lack of subcutaneous fat. The reflexes were normal.

The urine was normal chemically and microscopically and chromatography revealed no increase of amino acids. Examination of the blood showed: Hb 11 g. per 100 ml.; haematocrit 37%; M.C.H.C. 30%; W.B.C. 11,500 per c.mm. (neutrophils 22%, lymphocytes 78%, reticulocytes 4%, platelets present in normal numbers); prothrombin index 100%; modified Ide test negative; blood urea 20 mg. per 100 ml.; serum chloride 98 mEq per litre; serum sodium 135 mEq per litre; serum inorganic phosphorus 5·8 mg. per 100 ml.; serum calcium 8·4 mg. per 100 ml.; alkaline phosphatase 7·6 K.A. units; serum proteins 4·8 g. per 100 ml. (albumin 2·02, α_1 globulin 0·36, α_2 globulin 0·81, β globulin 0·65, and γ globulin 0·76 g. per 100 ml.).

The results of a battery of empirical liver function tests were: thymol turbidity 15·5 units; thymol flocculation +++; colloidal red ++; cephalin cholesterol flocculation +, and zinc sulphate turbidity 13·2 units.

The blood lipogram (average of two estimations) showed: α_1 and α_2 cholesterol 19%; β cholesterol 81%; total lipid 760 mg. per 100 ml.; phospholipids 240 mg. per 100 ml.; total cholesterol 148 mg. per 100 ml.; free cholesterol 52 mg. per 100 ml.; cholesterol esters 96 mg. per 100 ml.; percentage esters to total 65%; cholesterol

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FIGS. 1-3.—Lipodystrophy, muscular hypertrophy, protuberance of the abdomen and enlargement of the hands and feet are shown.

phospholipid ratio 0·62; total fatty acids 547 mg. per 100 ml.; neutral fats 312 mg. per 100 ml.

Repeated estimations of the fasting blood sugar concentration ranged from 36 to 56 mg. per 100 ml. Following the ingestion of 50 g. glucose the blood sugar concentration rose from a fasting value of 44 mg. per 100 ml. to 94, 112, 104, 88 and 80 mg. per 100 ml. in 30, 60, 90, 120 and 150 minutes respectively. The blood sugar response to a subcutaneous injection of 1:1,000 adrenaline (0·01 ml. per kg.), was a rise from a fasting level of 36 mg. per 100 ml. to 66, 76, 83 and 79 mg. per 100 ml. at 15, 30, 45 and 60 minutes respectively. An injection of glucagon (20 μg. per kg.) caused a rise in the blood sugar concentration from 58 mg. per 100 ml. to 104, 141, 66 and 58 mg. per 100 ml. at 15, 30, 60 and 90 minutes.

Repeated stool examinations revealed adequate amounts of trypsin and the absence of fat globules, starch granules. muscle fibres, parasites or bacterial pathogens. A four-day fat balance showed an absorption of 96% of ingested fat.

The cerebrospinal fluid was normal. The serum protein-bound iodine concentration was 5·5 μg. %. The urinary neutral 17-ketosteroids were 0·63 mg. per 24 hours and the 17-hydroxycorticosteroids 2·3 mg. per 24 hours. The urinary gonadotrophin excretion was less than 6 mouse units per 24 hours.

Vaginal smears showed a moderate number of intermediate squamous cells, some showing an oestrogenic effect in advance of that expected for the age of the child.

Radiographs of the heart, lungs, skull, vertebrae, pelvis and limbs were normal. The radiological bone age of approximately 3 years corresponded to the chronological age. A barium meal presented normal features. A pneumo-encephalogram was normal.

The electrocardiogram was normal. The electroencephalogram showed random theta and irregular slow wave activity dominating all leads. A minimal amount of random alpha activity was superimposed over the central and post-central areas. This was regarded as an abnormal record but with no asymmetry and no focal or episodic activity.

The mental age on the Vineland Social Maturity Scale was about 16 months, giving a quotient of around 50%.

At diagnostic laparotomy the absence of mesenteric fat was striking. The liver was found to be enlarged and smooth. Histological section revealed small foci of necrosis with infiltration of round cells and a heavy infiltration of round cells in some of the portal tracts. There were also foci of syncitial clumping of nuclei and generalized mild fatty infiltration and marked deposition of glycogen (Figs. 4 and 5).

Sections of abdominal muscle showed slight hypertrophy. A lymph node contained no glycogen. The skin showed a moderate increase of melanin and the cells were chromatin positive.

The ovaries were large and contained many immature follicles and in addition occasional follicular cysts without evidence of luteinization.

Author	Title	Apparent Age of Onset	Age When Seen by Author	Sex	Height*	Dystro
Present report	Lipodystrophic muscular hypertrophy	Birth	2 yrs 10 mths	F	90%	+
Hall *et al.*, 1936	Congenital muscular hypertrophy	Birth	Birth	M	90%	+
Donohue and Uchida, 1954	Leprechaunism	Birth	Birth	F	?	+
Berardinelli, 1954 (Case 2)	An undiagnosed endocrinometabolic syndrome	Birth	2 yrs 2 mths	M	90%	+
Seip, 1959 (Case 1)	Lipodystrophy and gigantism with associated endocrine manifestations	Birth	6 yrs	F	90%	−
Seip, 1959 (Case 2)	Lipodystrophy and gigantism with associated endocrine manifestations	Birth	1 yr	M	90%	−
Seip, 1959 (Case 3)	Lipodystrophy and gigantism with associated endocrine manifestations	Birth	11 mths	M		+
Schwartz *et al.*, 1960	Generalized lipoatrophy, hepatic cirrhosis, disturbed carbohydrate metabolism and accelerated growth (lipoatrophic diabetes)	Birth	14 yrs	F	90%	+
Corner, 1952	Lipoatrophic diabetes	10 mths	14 yrs	F	?	+
Fontan *et al.*, 1956	Hypertrophie musculaire généralisée à début précoce avec lipodystrophie faciale	14 mths	11 yrs	F	90%	+
Tizard, 1954	Generalized lipodystrophy	20 mths	2 yrs 7 mths	F	90%	+
Berardinelli, 1954 (Case 1)	An undiagnosed endocrinometabolic syndrome	? 2½ yrs	6 yrs	M	90%	+
Hansen and McQuarrie, 1940	Study of certain tissue lipids in generalized lipodystrophy	3 yrs	4 yrs	M		+
Murray, 1952 (Case 2)	Lipodystrophy	8 yrs	37 yrs	F		+
Murray, 1952 (Case 1)	Lipodystrophy	25 yrs	52 yrs	F		+
Lawrence, 1946	Lipodystrophy and hepatomegaly with diabetes	26 yrs	26 yrs	F		+
Ziegler, 1928	Lipodystrophies	27 yrs	27 yrs	F		+

* Standard used was growth chart devised by Stuart and Stevenson (1959).

Discussion

A number of cases identical to or closely resembling the one described have been previously reported but space does not permit their detailed appraisal. The main features appear in the Table and are further discussed below.

Lipodystrophy. In most patients there was an almost total absence of body fat and in our case absence of both mesenteric and perinephric fat was observed at laparotomy. In the less severely affected patients a specific pattern of loss of fat was seen affecting first the face and then progressively

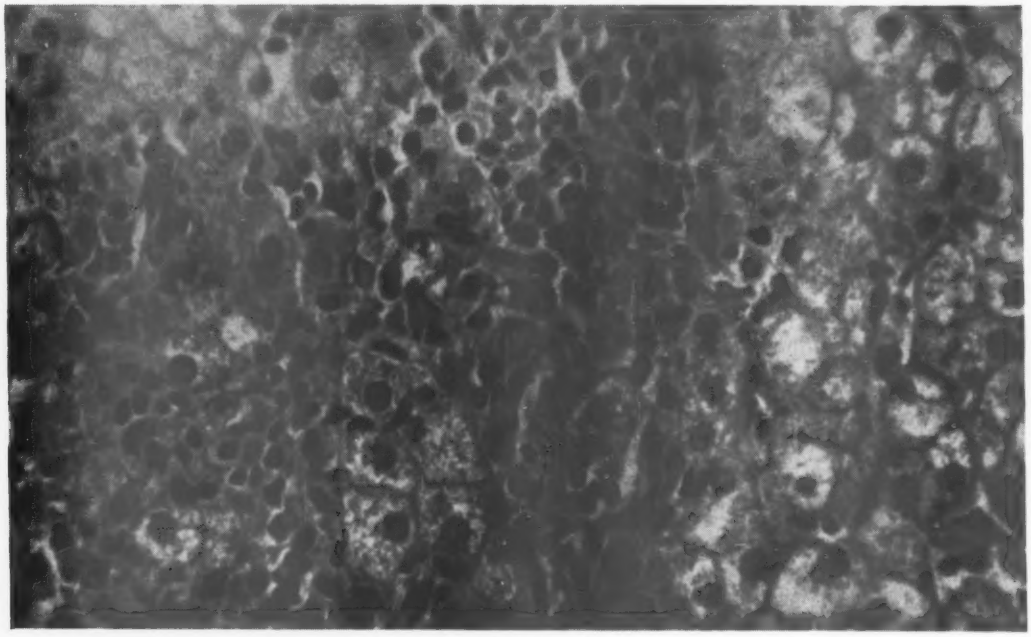

FIG. 4.—Photomicrograph showing section of liver with liver cells (rich in glycogen). In the centre there is a focus of round cell infiltration in relation to degenerating liver cells. (H. and E. ×453.)

Height	Lipodystrophy	Prominence of Muscles	Liver Involvement: Clinical Biochemical or Histological	Abnormal Blood Glucose Concentration	Big Hands and Feet	Genital Enlargement	Raised B.M.R.	Enlarged Kidneys
90%	+	+	+	+	+	+		
90%	+	+	+		+	+		
?	+	−	+		?+	+		+
90%	+	+	+	+	+	+		
90%	+	+	+		+	+		
90%	+	+	+		+	+		
	+	+	+		+	+		
90%	+		+	+				
?	+	+	+	+			+	+
90%	+	+	+			+	0	
90%	+	+	+					
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	+	+	+	+			+	
	+		+	+				
	+	+	+	+			+	+
	+	+	+	+			+	

the neck, arms and upper trunk with the lower trunk and legs unaffected or even showing increased fat deposition (Murray, 1952).

Muscle Enlargement. This was generalized and favoured no particular group. In some it was the most obvious feature at first glance, and imparted an athletic appearance. Muscle power appeared to accord with the enlargement.

Growth. The children tended to the 90th percentile or more for height and had enlargement

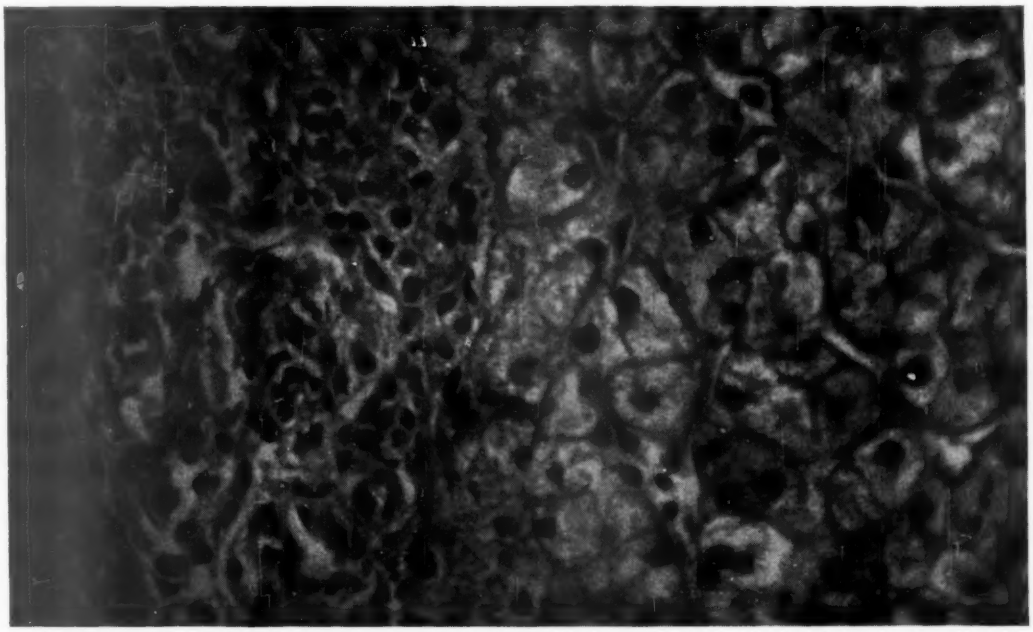

FIG. 5.—Photomicrograph showing section of liver with a portal tract (on the left) and periportal zone of liver lobule (on right). Round cell infiltration of the portal tract, and infiltration by these cells of the peripheral zone of liver lobule in relation to degenerating liver cells is shown. The liver cells on the right are rich in glycogen (confirmed by periodic acid–Schiff reaction and diastase response). (H. and E. ×453.)

of the hands and feet. Growth was unaffected in adults.

Derangements of Blood Sugar. A consistent pattern was not seen, but generally speaking hypoglycaemia was present in the young and hyperglycaemia in older subjects. The hyperglycaemia varied in degree from a raised glucose tolerance curve to severe diabetes which was insulin resistant. Ketosis was noticeably absent. Hyperplasia of the islets of Langerhans with an increased concentration of insulin in the pancreas was found in two infants (Donohue and Uchida, 1954) and there was increased plasma insulin activity in two other patients (Seip, 1959; Schwartz *et al.*, 1960).

Genitalia. Enlargement of the clitoris and of the penis was present in the younger patients without evidence of increased secretion of adrenal androgens or of pituitary gonadotropin. Genital differentiation was otherwise normal in the females and no other virilizing features were present. This most unusual genital effect was not evident in the adults. Enlargement of the ovaries with follicular cyst formation was also present. No information is available regarding testicular histology.

Liver. Hepatomegaly was present and the empirical tests of liver function abnormal. Microscopic examination of the liver showed progression from patchy areas of swollen fused liver cells with mild fatty infiltration and heavy deposition of glycogen to irregular fibrosis and eventual cirrhosis. This appeared to be the cause of death in two patients.

Kidneys. Information regarding renal size is only available in four patients of the series (Lawrence, 1946; Corner, 1952; Donohue and Uchida, 1954), and in all there was enlargement with no histologically obvious cause.

Basal Metabolic Rate. The B.M.R. was estimated in six patients, three of them children, and found elevated in four. The raised B.M.R. was not due to thyroid overactivity. There appeared to be some correlation between the severity of the syndrome and the B.M.R. level.

Serum Lipids. Hyperlipaemia was commonly present and fractionation suggested the increase was of the neutral fraction.

Hirsuties and Pigmentation. Generalized slight pigmentation and fine hirsuties was apparent in a number of the patients. Curliness of scalp hair was also mentioned.

It has been suggested that the primary defect causing this syndrome is one involving storage of fat (Lawrence, 1946; Schwartz *et al.*, 1960). However, in Lawrence's patient (Lawrence, 1946) the diabetes preceded the lipodystrophy and, moreover, it is difficult to understand how this defect could give rise to the other features. Again in partial lipodystrophy total fat stores are little altered, yet the other features are to be found (Murray, 1952).

The association of tallness, hirsuties, big hands and feet, mobilization of fat, increase of muscle mass, ovarian and genital enlargement and abnormal blood glucose concentrations strongly suggests a hormonal basis. However, no recognized hormone in man is known to produce this syndrome, although the major features, increased growth, increase in muscle mass, mobilization of depot fat and hypoglycaemia succeeded by hyperglycaemia have been induced by administration of 'growth hormone' pituitary extracts to animals (Astwood, 1955). In man an excess of growth hormone should produce gigantism in the child and acromegaly in the adult. Are there then two different growth hormones, the one causing acromegaly and the other the effects noted by physiologists and resembling the features present in the syndrome?

It is tentatively suggested, therefore, that the syndrome results from oversecretion of a hormone having many of the effects attributed to 'growth hormone' extracts, but with mobilization of fat as its major function.

Kekwick and co-workers (Kekwick, 1960) have isolated from the urine of fasting subjects a substance resembling corticotrophin that mobilizes fat in mice. This substance has also been found in the urine of two non-fasting subjects with diffuse lipoatrophy. It may well be that elucidation of the relationship between this substance and pituitary growth hormone extracts will solve the aetiology of 'lipodystrophic muscular hypertrophy'.

Whilst it is postulated that the syndrome results from a primary excess of hormone secretion, it is tempting to suggest that secondary hypersecretion of the same hormone may be provoked by obesity and in turn be responsible for the non-ketotic insulin-resistant diabetes commonly present in such overweight subjects.

From the Table it will be seen that this condition was noted in some instances at birth, whilst in others it manifested later in life. The patients have therefore been tentatively allocated into congenital and acquired groups. Although the congenital group is small (nine patients) the story of consanguinity in four families (Hall *et al.*, 1936; Berardinelli, 1954; Donohue and Uchida, 1954; Seip, 1959) two with

two children affected (Donohue and Uchida, 1954; Seip, 1959) strongly suggests a genetic basis. The apparent absence of the syndrome in the parents and its presence in children of both sexes may indicate a homozygous recessive autosomal gene state.

Until a pathophysiological name becomes possible, 'lipodystrophic muscular hypertrophy' describes the two most obvious presenting features.

Summary

A girl of 2 years and 10 months with a number of unusual features including lipodystrophy, generalized muscular hypertrophy, hepatomegaly with biochemical and histological evidence of disordered function, enlargement of the hands, feet and clitoris, abdominal protuberance and a lowered concentration of glucose in the blood, is described.

There are reports in the literature of patients who appear to have the same syndrome in either 'congenital' or 'acquired' form.

It is suggested that the syndrome results from hormonal action, possibly from the excessive secretion of a specific pituitary hormone.

'Lipodystrophic muscular hypertrophy' is proposed as the name for the syndrome.

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References

Astwood, E. B. (1955). 'Growth hormone and corticotropin.' In *The Hormones: Physiology, Chemistry and Applications*, ed. G. Pincus and K. V. Thimann, vol. III, p. 235. Academic Press, New York.

Berardinelli, W. (1954). An undiagnosed endocrinometabolic syndrome: Report of 2 cases. *J. clin. Endocr.*, **14**, 193.

Corner, B. D. (1952). Lipoatrophic diabetes. *Arch. Dis. Childh.*, **27**, 300.

Donohue, W. L. and Uchida, I. (1954). Leprechaunism: A euphuism for a rare familial disorder. *J. Pediat.*, **45**, 505.

Fontan, A., Verger, P., Couteau, J. M. and Pery, M. (1956). Hypertrophie musculaire généralisée à début précoce avec lipodystrophie faciale hépatomégalie et hypertrophie clitoridienne chez une fille de 11 ans. *Arch. franç. Pédiat.*, **13**, 276.

Hall, B. E., Sunderman, F. W. and Gittings, J. C. (1936). Congenital muscular hypertrophy. *A.M.A. Amer. J. Dis. Child.*, **52**, 773.

Hansen, A. E. and McQuarrie, I. (1940). Study of certain tissue lipids in generalized lipodystrophy: lipohistiodiaresis. *Proc. Soc. exp. Biol. (N.Y.)*, **44**, 611.

Kekwick, A. (1960). On adiposity. *Brit. med. J.*, **2**, 407.

Lawrence, R. D. (1946). Lipodystrophy and hepatomegaly with diabetes, lipaemia and other metabolic disturbances: a case throwing new light on the action of insulin. *Lancet*, **1**, 724, 773.

Murray, I. (1952). Lipodystrophy. *Brit. med. J.*, **2**, 1236.

Schwartz, R., Schafer, I. A. and Renold, A. E. (1960). Generalized lipoatrophy, hepatic cirrhosis, disturbed carbohydrate metabolism and accelerated growth (lipoatrophic diabetes). *Amer. J. Med.* **28**, 973.

Seip, M. (1959). Lipodystrophy and gigantism with associated endocrine manifestations: A new diencephalic syndrome? *Acta paediat. (Uppsala)*, **48**, 555.

Stuart, H. C. and Stevenson, S. S. (1959). Physical growth and development. In *Nelson Textbook of Paediatrics*, 7th ed. Saunders, Philadelphia and London.

Tizard, J. P. M. (1954). Generalized lipodystrophy. Infectious mononucleosis. Mild infantile hemiplegia. *Proc. roy. Soc. Med.*, **47**, 128.

Ziegler, L. H. (1928). Lipodystrophies. Report of seven cases. *Brain*, **51**, 147.

THREE DIFFERING CASES OF GLYCOGEN STORAGE DISEASE

BY

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More than 30 years have elapsed since von Gierke (1929) gave the first comprehensive account of clinical and pathological studies on cases in which large deposits of glycogen could be found in the liver and kidneys. Many cases have been reported since then and differing types of glycogen storage disease have been recognized so that a group of diseases each having their characteristic abnormalities is now known (Mason and Andersen, 1941; Cori, 1954). Recent advances in our knowledge of certain aspects of carbohydrate metabolism, in particular the enzymic synthesis and degradation of glycogen, has led to the belief that the group of diseases is caused by differing defects or deficiencies of certain enzymes, these abnormalities being controlled by genes of a mendelian recessive type.

The purpose of this report is to describe three cases of glycogen storage disease each of which has been the result of a consanguinous marriage. The three cases differ. Whilst it has not proved possible to perform all the desirable biochemical studies, observations on certain aspects of carbohydrate metabolism as revealed by intravenous galactose tolerance tests on the three cases are reported.

Case Reports

Case 1. H.M., an Iranian male, was first admitted to the Nemazee Hospital as an infant of 9 months in October 1958. The chief complaint was abdominal distension and diarrhoea. The mother's pregnancy and delivery of the baby had been normal. The infant developed jaundice at 3 days of age which seems to have been physiological, and an exanthem at 3 months of age was diagnosed as measles. About the same time the child had an episode of generalized convulsions lasting about 15 minutes, but the details are not clear. The mother noticed progressive abdominal distension and nocturnal low grade fever. Ten days before admission another episode of convulsions occurred during the night. It is stated that the child had had mild diarrhoea and occasional vomiting since birth which at one time necessitated a period of 25 days in hospital. The father is 32 years and the mother 20 years old. The parents are first cousins. The patient has a 4-year-old healthy sister and the only other sibling was a girl who died at 4 months of 'pneumonia'.

On admission the temperature was 36·5° C. and the respiratory rate was 33 per minute. The patient weighed 6·98 kg., his height was 65 cm. and the head circumference was 43 cm. He appeared small and undernourished but in no distress. The liver was palpable 7 cm. below the right costal margin and had a firm smooth consistency. There were no other positive physical findings.

Chest radiograph and barium swallow for oesophageal varices showed no abnormalities. An intravenous pyelogram showed moderate hydronephrosis of the right kidney. The liver appeared to be enlarged on the radiographs, but no splenomegaly was noted. The tuberculin test was negative. Urinalysis showed a moderate amount of acetone and a trace of albumin. The fasting blood sugar level ranged between 7 and 95 mg. per 100 ml., the total cholesterol ranged between 260 and 300 mg. per 100 ml. and CO_2 determinations gave values between 6 and 21 mEq per litre. Serum albumin was 5 g. per 100 ml. and serum globulin was 3 g. per 100 ml. Electrophoresis of the serum proteins was normal. Total bilirubin was 1·4 mg. per 100 ml. with a direct value of 0·25 mg. per 100 ml. The thymol turbidity was high, 23 units, but the cephalin-cholesterol flocculation test was negative. Haemoglobin was 12·1 g. per 100 ml. and the W.B.C. count was 13,200 per c.mm. with 15% segmented neutrophils, 76% lymphocytes and 9% monocytes. The prothrombin time was normal.

During the period in hospital the patient had repeated bouts of respiratory and urinary tract infections which were proven by cultures and treated by antibiotics. He had several episodes of hypoglycaemia and severe acidosis which could be relieved by frequent feedings with a high protein diet and by sodium bicarbonate. The biochemical studies were made when the patient was in a good condition and had been free of the above problems for several days.

An exploratory laparotomy was performed under general anaesthesia on December 2, 1958. There was

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massive enlargement of both lobes of the liver, which was soft in consistency and a pale pinkish yellow in colour. There was no peritoneal fluid. The spleen could not be palpated through the right upper quadrant incision and the gall bladder was normal. A biopsy specimen of liver tissue was obtained and the patient tolerated the whole procedure quite well. Histological examination of the liver tissue showed parenchymal cells that contained much fat (stained with Oil red O). The fat cells ranged from small to medium to large; fat cysts were present in some regions. Many parenchymal cells had a clear cytoplasm. These cells contained a PAS positive substance which did not react with PAS after incubation of the tissue preparations with diastase. There was moderate fibrosis but no evidence of cirrhosis.

After discharge from hospital, frequent out-patient examinations showed continued poor development and susceptibility to infections, acidosis and hypoglycaemia.

On September 21, 1959, the patient was readmitted to the hospital for the last time with severe pneumonia and in a comatose state. He did not respond to various kinds of supportive therapy, including antibiotics, intravenous glucose and alkali, and oxygen. He died on September 26, 1959. An autopsy could not be performed.

Case 2. A.D., an Iranian male, was brought to the Nemazee Hospital in January 1958, when 2 years old. He was the product of a normal pregnancy and delivery except for a few days spotting during the second month. The parents noted some protuberance of the abdomen mainly in the right upper quadrant at 2 months of age and this had been progressive particularly during the six months before admission. The child's appetite, feeding and development were described as normal. Four or five attacks of mild diarrhoea occurred during the first year of life. He had a bout of otitis media when 18 months old which had been treated successfully.

The parents were first cousins. The mother had had a total of seven pregnancies, four children still being alive. These included the patient, one healthy boy and two healthy girls. Of the three children who had died, one is said to have had the same kind of abdominal distension and died of an unknown cause when 2 years old. There is no history of abortions. The family lived in a village, drank well water and were poor economically.

On admission the temperature was 37·2° C. (rectally), the pulse rate 120 per minute, respirations 22 per minute, weight 7·05 kg., and head circumference 44 cm. The child appeared underdeveloped, undernourished and chronically ill, but in no acute distress. The teeth were carious. The protuberant abdomen on palpation revealed a large firm non-tender mass filling the right abdomen down to the iliac crest and extending obliquely to a point about three finger breadths below the right costal margin. Rectal examination was non-contributory.

X-ray studies including chest examination, barium enema, upper gastrointestinal series and intravenous pyelogram were all negative. The haemoglobin was 10·6 g. per 100 ml. and the W.B.C. count was 11,750 per c.mm. The urine was yellow and cloudy, had an acid *p*H and always contained acetone. A trace of albumin and a trace of sugar was detected on one occasion. The fasting blood sugar level ranged between 50 and 85 mg. per 100 ml. and the blood cholesterol was 420 mg. per 100 ml. The thymol turbidity was again high, 27 units, but the cephalin-cholesterol flocculation test was negative. The tuberculin test was negative. Further biochemical studies will be described later.

An exploratory laparotomy was performed and revealed a huge liver extending into the right lower quadrant. All the lobes were enlarged and the liver surface was smooth and pale. A biopsy sample was taken. The abdomen contained a minimal amount of fluid, a culture of which was negative. There appeared to be some ascaris in the small bowel. During surgery the patient developed marked slowing of the heart, but soon recovered and the condition became satisfactory. The post-operative course was uneventful.

Histological examination of the liver specimen showed parenchymal cells that were quite large, but variable in size and shape with a clear cytoplasm. Tissue sections were stained with Oil red O and PAS before and after incubation with diastase. The sections stained for fat showed minimal droplets scattered throughout the parenchymal cells; the droplets were not large. The sections stained with PAS were positive before but negative after incubation with diastase. There were occasional fine strands of fibrous connective tissue extending from the portal regions into scattered lobules, but there was no cirrhosis.

The patient left the hospital in March 1958, in good condition having gained 3 lb. whilst in hospital, but contact with this patient has since been lost.

Case 3. Z.E., an Iranian girl, was brought to the Nemazee Hospital in October 1957, when 4½ years old because of enlargement of her abdomen. Pregnancy and delivery had been normal. The child had been breast fed for only three months and had then been placed on whole cow's milk. Development had been slow. She sat up at 1 year, began to talk at 2 years and to walk at 3 years of age. She was well during the first six months of life, but then enlargement of the abdomen was first noticed. About the same time a skin infection had developed on her back which improved after six months of therapy. She had an attack of otitis at 3½ years of age and had had a few minor respiratory infections. The enlargement of the liver was described as having been progressive until the time of admission to hospital. The one remarkable fact about the family history was that the parents were second cousins.

On admission physical examination showed a temperature of 36·4° C. (axilla), pulse rate 120 per minute, respirations 34 per minute, weight 10 kg. and height 76 cm. The child appeared to be underdeveloped, but otherwise well nourished, was a little obese but did not look ill. The only positive physical findings were the markedly protuberant abdomen and a firm non-tender liver extending 6 cm. below the right costal margin.

The liver had a smooth surface and a firm consistency. Rectal and neurological examinations were within normal limits. Various radiological studies including chest films, intravenous pyelogram, barium enema and bone survey were negative except for the enlarged liver.

The haemoglobin was 11·5 g. per 100 ml. and the W.B.C. count was 18,100 per c.mm., with 36% polymorphs, 63% lymphocytes and 1% monocytes. The prothrombin time was normal. The tuberculin test was negative. Urinalysis revealed a straw-coloured urine of acid *p*H, specific gravity 1,015 containing neither albumin nor sugar, but significant amounts of acetone were always present. The fasting blood sugar ranged between 60 and 120 mg. per 100 ml., the blood cholesterol was 190 mg. per 100 ml. and CO_2 was 16·2 mEq per litre. Serum albumin was 4·0 g. per 100 ml. and serum globulin 2·0 g. per 100 ml. Thymol turbidity was 3·5 units and the cephalin-cholesterol flocculation was 1+ after 48 hours. The total serum bilirubin was 0·2 mg. per 100 ml. The various tests on carbohydrate metabolism will be presented in a separate section.

An exploratory laparotomy was performed on November 16, 1957, which revealed a large liver with normal surface, colour and shape. There was about 10 ml. of clear fluid in the abdomen which gave a negative result on culture. The spleen was not enlarged and the rest of the abdominal organs appeared normal. The surgical procedure was tolerated well and the post-operative period was uneventful. A liver biopsy was obtained and histological examination showed changes essentially the same as in Case 2.

A muscle biopsy was obtained from the right gastrocnemius on December 4, 1957, under general anaesthesia. The muscle looked normal grossly and microscopic examination of the histological preparations revealed normal muscle tissue with no significant changes.

On March 11, 1958, a second laparotomy was performed and a liver biopsy specimen was taken for the estimation of glucose-6-phosphatase activity. Unfortunately, insufficient liver tissue was obtained to permit an estimation of the liver glycogen content. At this time the surgeon noted that the liver was appreciably larger than at the first laparotomy. Again there was some sterile serous fluid in the peritoneal cavity. Histological examination of the second biopsy specimen showed changes similar to those in the original material.

The child is being seen regularly in our clinic and is doing well except for a severe bout of pneumonia in May 1959, from which she recovered uneventfully. At this time she weighed 13·6 kg. and the liver was noted to be about 8 cm. below the right costal margin. On her last visit to hospital in May 1960, for a mild otitis media, she was in excellent general health and weighed 16·1 kg.

Studies on Carbohydrate Metabolism

Materials and Methods. The samples of liver tissue which were taken during laparotomy or at autopsy were frozen solid using dry ice and stored at −20° C. for not more than 24 hours until the assays of glucose-6-phosphatase activity were performed essentially by the method of Cori and Cori (1952) except that sodium citrate was used instead of potassium citrate and inorganic phosphate was determined by the method of Fiske and Subbarow (1925).

In the various tolerance tests to be described, blood was taken by heel puncture and withdrawn into a heparinized pipette. Glucose or total reducing sugar was determined by the Sunderman-Fuller macrotechnique described by Sunderman, Copeland, Macfate, Martens, Naumann and Stevenson (1956) after removal of the proteins with sulphuric acid and sodium tungstate. Galactose was determined after the removal of glucose by fermentation with yeast according to the method described by King and Wootton (1956). In the galactose tolerance tests, glucose was determined as the difference between the total reducing sugar and the equivalent reducing power of the galactose. Lactic acid was determined by the method of Barker and Summerson (1941) on the sulphuric acid sodium tungstate filtrates.

TABLE 1

ASSAYS OF GLUCOSE-6-PHOSPHATASE ACTIVITY IN LIVER BIOPSY SPECIMENS OF THE THREE CASES AND TWO NORMAL LIVER CONTROLS

Liver Tissue in Incubation Mixture (mg./ml.)	Inorganic Phosphatase Liberated (µg. P/100 mg. tissue)				
	Case 1	Case 2	Case 3	Normal A	Normal B
40	11	145	199	268	27(
20	18	166	264	449	41(
8	33	212	323	664	55(

Glucose-6-phosphatase Assays. The results are shown in Table 1, which includes assays under identical conditions on liver samples from two control subjects who were undergoing laparotomy for other reasons. As noted by Cori and Cori (1952), less liver homogenate showed rather more than proportional effect. The results indicated marked differences between the three cases.

Glucose and Adrenaline Tolerance Tests. The amount of glucose administered intravenously was 1 g. per kg. body weight and adrenaline was given intramuscularly. The results of the tests are shown in Tables 2 and 3

TABLE 2

GLUCOSE TOLERANCE TESTS ON CASES 1, 2 AND 3: ALL FIGURES ARE mg. GLUCOSE per 100 ml. WHOLE BLOOD

Time (min.)	Case 1	Case 2	Case 3
0	10	50	60
2	—	150	—
15	116	120	—
30	88	100	120
45	60	50	—
60	46	45	76
90	36	—	—
120	—	—	76
180	—	—	76
240	—	—	64

TABLE 3

ADRENALINE (EPINEPHRINE) TOLERANCE TESTS ON CASES 1, 2 AND 3: ALL FIGURES ARE mg. GLUCOSE per 100 ml. WHOLE BLOOD

Time (min.)	Case 1		Case 2	Case 3
	Test a	Test b		
0	3	32	50	76
15	2	24	65	86
30	8	22	60	100
60	4	12	80	100
120			60	70

respectively. The glucose tolerance tests showed typical behaviour. In Case 1 there was no response to adrenaline, but Cases 2 and 3 showed small but significant increases in blood glucose following adrenaline administration.

Intravenous Galactose Tolerance Tests. In each test 1 g. of galactose per kg. body weight was administered intravenously during the course of two to three minutes in the form of a 20% aqueous sterile solution. The results for the three cases are shown in Figs. 1, 2 and 3 respectively. During the course of the tests, serious signs of acidosis were noted only in Case 1 where the lactic acid level was greatly elevated. The acidosis was controlled with sodium bicarbonate.

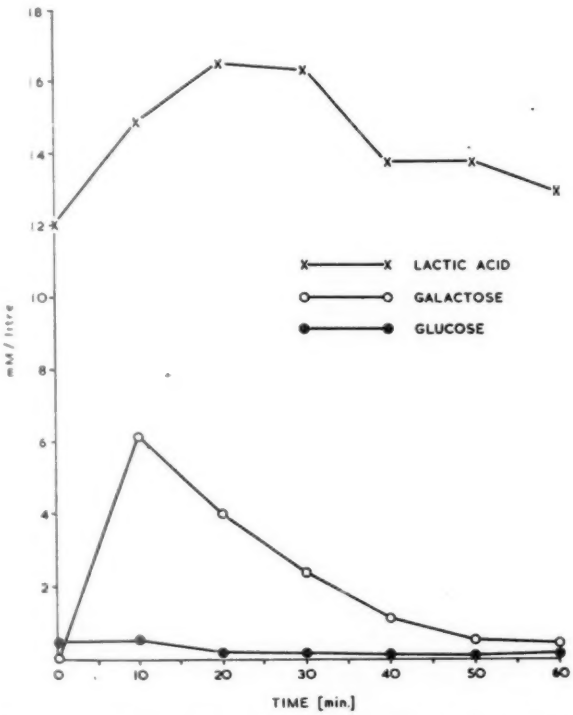

FIG. 1.—Galactose tolerance test on Case 1. Galactose (1 g. per kg.) was administered intravenously immediately after taking the zero time blood sample and over the course of the first three minutes. Further blood samples were taken at the times shown and assayed (see text).

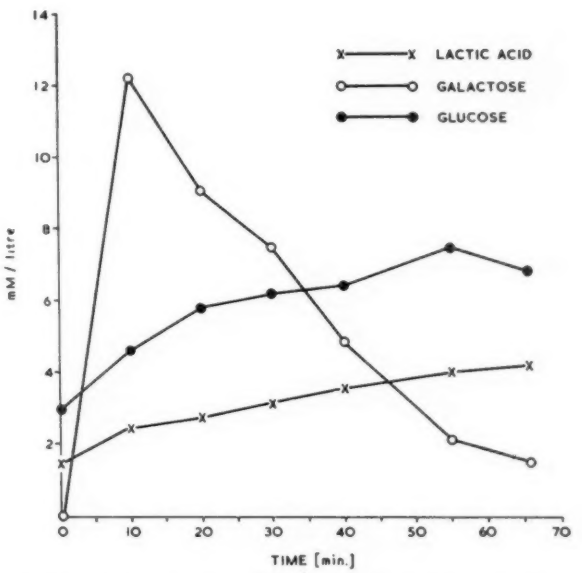

FIG. 2.—Galactose tolerance test on Case 2. Details as in Fig. 1.

Discussion

The family histories in all these cases are striking in that there is a history of consanguinity and also because of the possible occurrence of the disease in a sibling of Case 1 (H.M.) who had died at

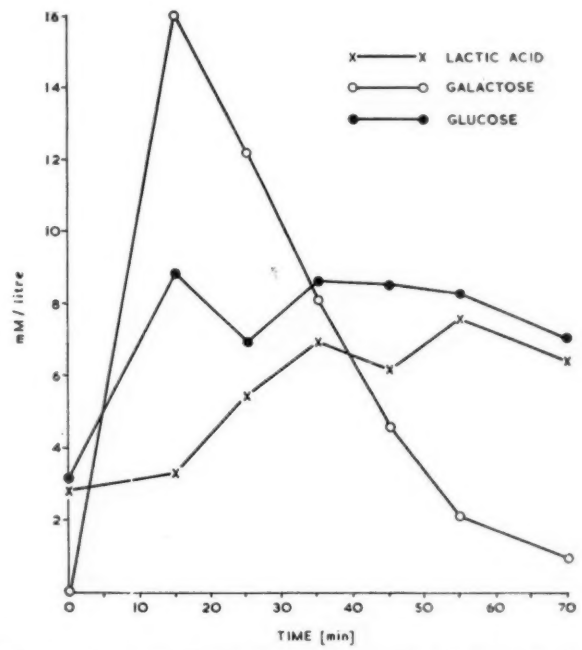

FIG. 3.—Galactose tolerance test on Case 3. Details as in Fig 1.

4 months of age of 'pneumonia', and in a sibling of Case 2 (A.D.) who had died with hepatomegaly. Unfortunately it has not proved possible to obtain very accurate information from the parents. These cases give strong support to the concept (van Creveld, 1939) that glycogen storage disease is transmitted by a recessive gene.

The diagnosis in all the cases of glycogen storage disease was based upon the clinical finding of poor development and hepatomegaly and the attacks of convulsions in Case 1 which were probably due to hypoglycaemic episodes. The laboratory findings of acetonuria and varying degrees of hypoglycaemia in all three cases as well as the microscopic examination of the liver biopsy specimens and the more extensive biochemical studies seem to establish the diagnosis on firm grounds.

The three cases were different. Our first case represented the severe and classical form of von Gierke's disease both from the points of view of clinical history and laboratory findings. Cases 2 and 3 were less severe cases from the clinical point of view and are alive and comparatively well. Andersen (1957) remarked that the variations in the degree of severity of the disease could be attributed mainly to variations in the glucose-6-phosphatase activity of the liver. This enzymic activity in our cases is discussed further below, but the almost normal level of glucose-6-phosphatase activity in Case 3 is one of several similarities to an atypical case described by Zetterström and Sörbo (1956) except that fat was not a prominent feature in our case. In fact, Cases 2 and 3 were indistinguishable histologically as against Case 1 which had the added feature of abundant fat in the liver including fat cysts. The absence of any cirrhosis in Case 3 excludes the possibility of it being a case with a glycogen of abnormal structure due to a deficiency of the 'branching' enzyme (amylo-1:4——→1:6 trans-glucosidase).

The results of the glucose-6-phosphatase assays revealed distinct differences between the three cases and confirmed the very severe condition of Case 1. In Case 2, the enzymic activity was certainly not so low as in Case 1, but the values were below those of the normal controls and within the range of abnormal values quoted by Cori (1954). The glucose-6-phosphatase activity in Case 3 was higher than for the other two cases and clearly indicated that, while the activity was not quite so high as in the two normal controls, there was sufficient enzyme present to catalyse a significant production of glucose from glucose-6-phosphate. Cori (1954) also mentioned two cases of glycogen storage disease in which the glucose-6-phosphatase activity was almost normal. Storage of glycogen in increased quantities in the liver is therefore possible even in the presence of considerable amounts of the enzyme.

The intravenous glucose tolerance tests and the adrenaline tolerance tests agreed with the other findings. The use of galactose to examine the carbohydrate metabolism of these cases was employed by Mason and Andersen (1955) who fed galactose orally to a patient with von Gierke's disease and observed only a very small increase in the blood sugar level. Schwartz, Ashmore and Renold (1957) performed both oral and intravenous galactose tolerance tests on a patient in whom no production of inorganic phosphate could be demonstrated when a liver homogenate was incubated with glucose-6-phosphate. Using the oral test, these authors confirmed the findings of Mason and Andersen (1955) of very little increase in blood sugar level and marked lactic acidosis. Using the intravenous galactose tolerance the lactic acidosis was again seen and there was no formation of glucose from galactose. This latter result agreed with the finding of no glucose-6-phosphatase activity. In Case 1 of the present study in which glucose-6-phosphatase activity was again very low, the results of the galactose tolerance test (Fig. 1) were very similar to those described by Schwartz *et al.* (1957), thus providing confirmatory evidence that this functional test might be used as a helpful diagnostic test for severe hepatorenal glycogen storage disease. However, in Case 2, diagnosed clinically as a less severe form of the same disease, the intravenous galactose tolerance test was different. There was slow steady production of glucose from galactose as might be expected from the demonstrated presence of some glucose-6-phosphatase activity. In Case 2 the initial lactic acid level was much lower than in Case 1 and the rate of lactic acid production was much less (Fig. 2). Thus the use of the intravenous galactose tolerance test as a diagnostic procedure for von Gierke's disease appears to be confined to cases where the glucose-6-phosphatase activity is very low or absent. It is also clear that those cases with a certain amount of glucose-6-phosphatase activity can form glucose even if in decreased quantities.

It is difficult, therefore, to see why there should be such excessive storage of glycogen in those cases with only some decrease in glucose-6-phosphatase activity. Formation of glucose from other sources such as amino acids has been described in cases of this type before. Lowrey and Wilson (1949) were able to raise the blood sugar level in a severe case by feeding gelatin. In Case 2, glucogenesis from galactose definitely occurred even though in reduced

amounts compared to a normal individual. This implies that the problem of the source of the blood glucose in cases of von Gierke's disease may be confined largely to those cases where the glucose-6-phosphatase activity is very low or absent.

The intravenous galactose tolerance test on Case 3 (Fig. 3) showed an immediate sharp rise in the blood glucose level resembling that demonstrated by Schwartz *et al.* (1957) on a normal child. A small increase in lactic acid was noted which differed from the normal case quoted, thus showing that the carbohydrate metabolism was not entirely normal in our atypical case. The lactic acid production is probably due to the high liver glycogen content preventing the normal conversion of galactose to glycogen. Case 3 is therefore of a type in which glycogen storage disease can arise and yet there be almost normal glucose-6-phosphatase activity and production of glucose from galactose. This seems to us to indicate that the glucose-6-phosphatase theory for von Gierke's disease does not apply in certain atypical cases. It would be interesting to know the results of the intravenous galactose tolerance test on the cases quoted by Cori (1954) and Zetterström and Sörbo (1956). It could be that the genetic defect is still concerned with glucose-6-phosphatase but that, in certain atypical cases, alternative pathways of metabolism are developed to an increased extent.

This discussion so far has assumed that the milder forms of glycogen storage disease as seen in Cases 2 and 3 are due to the same genetic defect as the classical form of von Gierke's disease. These atypical cases may, however, be due to a deficiency of some other enzyme. Calderbank, Kent, Lorber, Manners and Wright (1960) have shown that in von Gierke's disease the liver contains high concentrations of the associated enzymes that act upon glucose-6-phosphate, namely phosphoglucomutase, glucose-6-phosphate dehydrogenase and phosphoglucose-isomerase. Synthesis of glycogen by a uridine diphosphate transferase system has been described by Leloir and Cardini (1957) in rat liver and by Hauk and Brown (1959) in rabbit muscle tissue. Hauk, Illingworth, Brown and Cori (1959) have shown that a deficiency of this enzyme cannot account for the generalized type of glycogen storage disease which also involves muscle tissue.

Hers (1959; 1960) has offered evidence which suggests that a deficiency of the 'debranching' enzyme (amylo-1:6-glucosidase) may be the defect in these apparently mild cases of glycogen storage disease. He has shown, using a radio-isotope technique unlikely to be available to many clinical laboratories, that liver tissue from several cases with only a slightly lower than normal assay for glucose-6-phosphatase has a virtually complete absence of amylo-1:6-glucosidase activity. A few other cases showed a deficiency in phosphorylase activity. This does suggest that such milder cases are due to a different defect from that in the classical form of von Gierke's disease. The defect is presumably due to a different gene which is probably also of the recessive type.

The results described also tend to confirm that the liver is the source of the lactic acid formed. Galactose is taken up rapidly from the systemic blood presumably by a galactokinase system in the liver. The galactose-1-phosphate thus formed will be converted via glucose-1-phosphate to glucose-6-phosphate. Because the glucose-6-phosphate cannot be directly hydrolysed at the normal rate, increased glycolysis might be expected to occur which results in lactic acid production. This appears to be the only explanation of the increases in lactic acid levels after galactose administration. The lactic acid curve in Case 1 shows that lactic acid was being utilized towards the end of the experiment presumably by muscle and other peripheral tissues (Andersen, 1957). This can serve as an alternative and additional source of energy for these tissues. The demonstration of lactic acid utilization also shows how sodium lactate could still be used to treat acidosis in spite of the already high level of blood lactic acid.

Summary

Three differing cases of glycogen storage disease are described. Each arose from a consanguinous marriage. One was a case of the classical von Gierke's disease, but the other two were less severe cases. The galactose tolerance test was used to investigate certain aspects of carbohydrate metabolism in the patients and the results are discussed in the light of recent biochemical knowledge of carbohydrate metabolism.

References

Andersen, D. H. (1957). Miscellaneous disorders of metabolism: V. Glycogen storage diseases and galactosaemia. In *Biochemical Disorders in Human Disease*, ed. R. H. S. Thompson and E. J. King. Churchill, London.

Barker, S. B. and Summerson, W. H. (1941). The colorimetric determination of lactic acid in biological material. *J. biol. Chem.*, **138**, 535.

Calderbank, A., Kent, P. W., Lorber, J., Manners, D. J. and Wright, A. (1960). Biochemical investigation of a case of glycogen-storage disease (von Gierke's disease). *Biochem. J.*, **74**, 223.

Cori, G. T. (1954). Glycogen structure and enzyme deficiencies in glycogen storage disease. *Harvey Lect.*, **48**, 145.

—— and Cori, C. F. (1952). Glucose-6-phosphatase of the liver in glycogen storage disease. *J. biol. Chem.*, **199**, 661.

van Creveld, S. (1939). Glycogen disease. *Medicine (Baltimore)*, **18**, 1.

Fiske, C. H. and Subbarow, Y. (1925). The colorimetric determination of phosphorus. *J. biol. Chem.*, **66**, 375.

von Gierke, E. (1929). Hepato-nephromegalia glykogenica (Glykogenspeicherkrankheit der Leber und Nieren). *Beitr. path. Anat.*, **82**, 497.

Hauk, R. and Brown, D. H. (1959). Preparation and properties of uridinediphosphoglucose-glycogen transferase from rabbit muscle. *Biochim. biophys. Acta*, **33**, 556.

——, Illingworth, B., Brown, D. H. and Cori, C. F. (1959). Enzymes of glycogen synthesis in glycogen-deposition disease. *Ibid.*, **33**, 554.

Hers, H. G. (1959). Études enzymatiques sur fragments hépatiques. Application à la classification des glycogénoses. *Rev. int. Hépat.*, **9**, 35.

—— (1960). Amylo-1:6-glucosidase activity in tissues of children with glycogen-storage disease. *Biochem. J.*, **76**, 69P.

King, E. J. and Wootton, I. D. P. (1956). *Micro-analysis in Medica Biochemistry*, 3rd ed. Churchill, London.

Leloir, L. F. and Cardini, C. E. (1957). Biosynthesis of glyco en from uridine diphosphate glucose. *J. Amer. chem. Soc.*, **79**, 6 40.

Lowrey, G. H. and Wilson, J. L. (1949). Observations on the t at- ment of a case of glycogen storage disease. *J. Pediat.*, **35**, 70 .

Mason, H. H. and Andersen, D. H. (1941). Glycogen dise se. *Amer. J. Dis. Child.*, **61**, 795.

—— —— (1955). Glycogen disease of the liver (von Gier e's disease) with hepatomata. *Pediatrics*, **16**, 785.

Schwartz, R., Ashmore, J. and Renold, A. E. (1957). Galac ose tolerance in glycogen storage disease. *Ibid.*, **19**, 585.

Sunderman, F. W., Copeland, B. E., Macfate, R. P., Martens, V E., Naumann, H. N. and Stevenson, G. F. (1956). Manua of American Society of Clinical Pathologists workshop on glu ose (condensed version). *Amer. J. clin. Path.*, **26**, 1355.

Zetterström, R. and Sörbo, B. (1956). Glycogen storage disea of the liver. *Acta paediat.* (*Uppsala*) **45**, 269.

A CASE OF PRECOCIOUS PUBERTY IN A FEMALE

BY

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Sexual precocity is considered to be present when indications of genital maturation become apparent in boys before the age of 10 years and in girls before the age of 8 years (Seckel, 1946). It is customary to divide these cases into two groups. In those with true precocious puberty maturation with spermatogenesis or ovulation has occurred in a normal manner, but at an abnormally early age; in those with pseudoprecocious puberty, premature development of the secondary sex organs, but without spermatogenesis or ovulation, has occurred as a result of an ovarian or adreno-cortical tumour, unusual sensitivity of end-organs to normal hormonal stimulation, or exogenous application of sex hormones or other compounds (Talbot, Sobel, McArthur and Crawford, 1952). In a small proportion of cases true precocious puberty is associated with tumours or cysts in the region of the hypothalamus or with post-meningitic or post-encephalitic lesions, but in the majority diligent and repeated search fails to reveal any abnormality in the nervous system or endocrine glands (Wilkins, 1957). Such cases are generally referred to as 'idiopathic' or 'constitutional' (Novak, 1944), and it is suggested that the genetic factor or factors that determine the time of hypothalamic sex maturation must be at fault (Seckel, 1946). In a small percentage of cases there is a heredo-familial tendency (Rush, Bilderback, Slocum and Rogers, 1937; Jacobsen and Macklin, 1952).

Precocious puberty of idiopathic origin represents simply the early appearance of normal phenomena, and many of the physical and laboratory examinations reveal findings normal for older children (Lloyd, Lobotsky and Morley, 1950). Except for the hazard of precocious pregnancy and the possibility of subnormal stature, the prognosis of girls with idiopathic precocious puberty is good, and it does not appear that the menopause is accelerated or that premature senility occurs (Talbot *et al.*, 1952; Jolly, 1955).

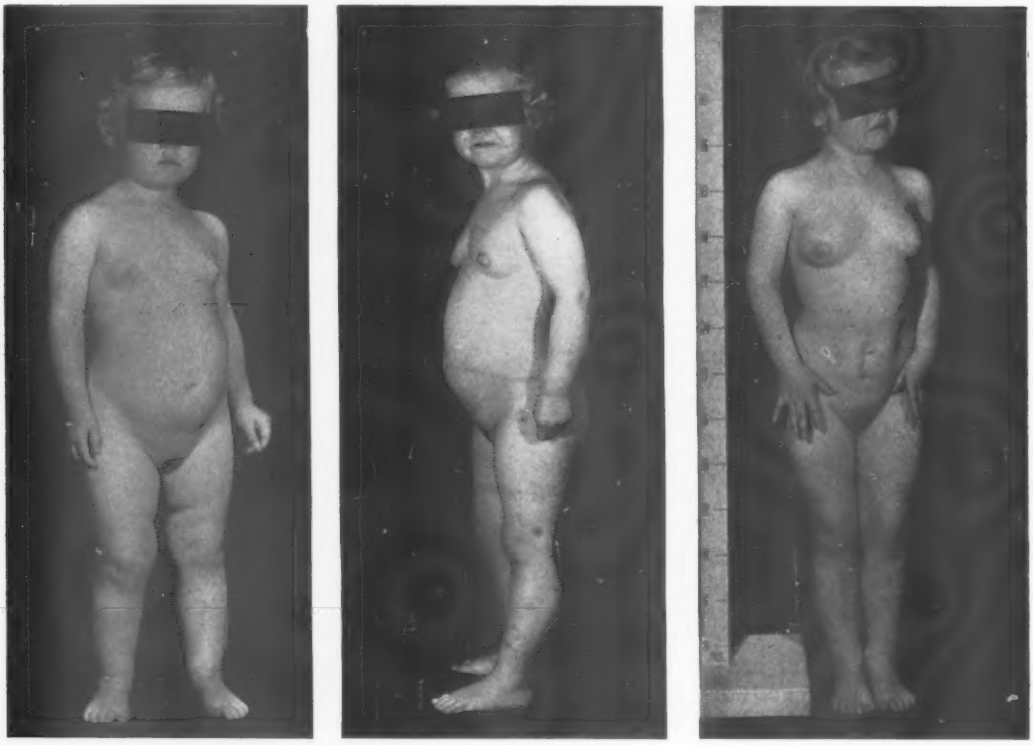
The following case of precocious puberty occurring in a female child appears to present features of sufficient interest to warrant publication.

Case History

The infant was born on July 15, 1953, the youngest of a family of six; she has three brothers, aged 13, 7 and 5 years, and two sisters, 11 and 3 years, all of whom show normal development. The birth weight was 8 lb. 14 oz. and during the first four or five months her progress followed the expected course. About the age of 5 months, however, enlargement of the nipples was first noticed, to be followed shortly afterwards by commencing breast development and the appearance of pubic hair. Two menstrual periods, each of two days' duration, then occurred at the age of 9 and 11 months.

At the age of 20 months she was first admitted to the Dunedin Hospital for investigation. The height was then 35 in. and the weight 35 lb. The facial expression was extremely mature for an infant of 20 months, while the stature was that of a stocky child of considerably older age (Fig. 1a). Breast development was proceeding, the areolae and nipples being already well developed. There was a growth of fine pubic hair and the external genitalia were typical of early adolescence. The clitoris was not enlarged. Neurological and radiological examination revealed no evidence of a cerebral tumour, and nothing abnormal was palpable within the abdomen. On rectal examination the cervix and uterine body were felt distinctly, and appeared to be well developed. No swelling was detected in the fornices suggestive of an ovarian tumour. The skeletal age determined radiologically was 4½ years (Gray, 1935). The 72-hour excretion of 17-ketosteroids was 0·3 mg. Since no evidence had been elicited inconsistent with a diagnosis of idiopathic or constitutional precocity, the child was sent home.

At the age of 27 months she was readmitted for further investigation and assessment. The facial expression and general bodily build were at this time considerably more mature than on the occasion of the first examination seven months previously (Fig. 1b), while breast and genital development had both progressed well into the adolescent stage. During this interval of seven months the height increment had been equivalent to approximately 15 months of average growth at this age and the weight increment to 18 months (Stuart and Stevenson, 1959). The most significant feature, however, was the extent of the skeletal development, which in seven months had progressed by 5½ years to reach the equivalent of 10 years (Gray, 1935). Although repeated examinations still failed to reveal any evidence



(*a*) (*b*) (*c*)

FIG. 1.—The child (*a*) 1 year 8 months; (*b*) 2 years 3 months; (*c*) 3 years 3 months.

inconsistent with the diagnosis of constitutional precocious puberty, in order to confirm this diagnosis it was decided to explore the pelvic organs surgically, and at the same time to palpate the adrenal glands. On the day before operation it happened that the child had her third menstrual period. At operation the uterus was found to have developed precociously, the body being larger than the cervix. There was no evidence of any ovarian tumour, but the left ovary was larger than the right and contained a recent corpus luteum and also a small follicular cyst deep in its substance. Nothing abnormal could be felt in the adrenal areas. A wedge of tissue removed showed normal cellular ovarian stroma, scattered throughout which were numerous primitive follicles with no histological evidence of neoplasm or other abnormality. The fourth menstrual period occurred six weeks later, since when periods have recurred without intermission every 28 days. Each is preceded by a few hours of lower abdominal discomfort and lasts for three to four days.

The child has since been admitted to the Dunedin Hospital on four occasions for reassessment of physical and mental development, the more important features of which have been summarized in Table 1. Some of these features will now be considered in more detail.

Physical Development

Growth in Weight and Height. Reference to the records kept by the Plunket infant welfare nurse showed that for the first four months growth in both weight (Fig. 2) and length had followed the expected course for an infant of slightly above average birth weight. During the remainder of the first year, however, when deceleration in growth normally occurs, increase in

TABLE 1

SUMMARY OF CHILD'S PHYSICAL AND MENTAL DEVELOPMENT

Chronological Age	6 months	9 months	1 year	1 year 8 months	2 years 3 months	3 years 3 months	4 years 2 months	5 years 9 months	6 years 11 months
Weight (lb.)	21	26½	30	35	42	52	63	79	82½
Height (in.)	26¾	29½	31	35	39	44	47½	52	53½
Skull circumference (in.) ..	17¼	18	—	19	—	20¼	—	21¼	21½
Bone age (years)	—	—	—	4½	10	14	15½	17	18
Dental age (years)	—	—	—	1½	—	—	4	6½	7
Mental age (years)	—	—	—	—	2 11/12	4½	6	7 6/12	9½

weight had continued at an almost uniform rate, with the result that at the age of 12 months the child's weight of 30 lb. was about 5 lb. in excess of the expected weight. Her length at this age was 31 in., also slightly above the average.

During the subsequent four and a half years growth in both weight and height were unusually rapid (Fig. 1c), so that at the age of 5 years 9 months her weight corresponded with that of an average New Zealand girl of 10 years, and her height with one of 8½ years (New Zealand Department of Health, 1956). Measurements taken 14 months later indicated, however, that this phase of rapid growth was by then coming to an end, and in particular that little further increase in height could be expected. Although early acceleration in growth had to some extent compensated for this premature cessation, it was obvious that the child would inevitably remain short in stature. During this latter period, also, she had lost much of the plumpness frequently associated with adolescence, and now had become much slighter in build.

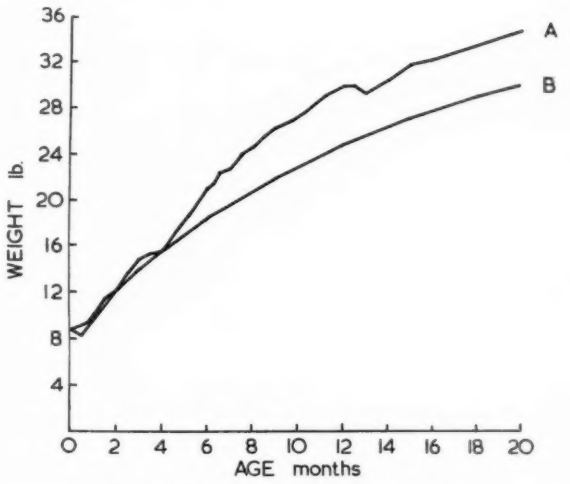


FIG. 2.—Weight–age curves to 20 months:
A—The child's weight–age curve;
B—Expected weight–age curve for infant of birth weight 8 lb. 14 oz. (From N.Z. Plunket Society's graph.)

TABLE 2

SKELETAL AGE, DETERMINED BY REFERENCE TO VARIOUS PUBLISHED NORMS

Chronological Age Year	Month	Region Examined	Skeletal Age (years) Flecker (1942)	Gray (1935)	Greulich and Pyle (1959)
1	8	Hand	5	4½	6½
2	3	Hand	8	10	9½
3	3	Elbow	11	14	—
4	2	Elbow	13	15½	—
5	9	Elbow	14	17	—
6	11	Shoulder and pelvis	20	18	—

Skeletal Development. One of the most striking features of this case was the pattern of skeletal development (Table 2). After an initial period of extremely rapid epiphyseal development the rate of skeletal maturation had approximated to the normal, but with the bone age consistently about 11 years in advance of the chronological age (Fig. 3). The closure of the upper femoral epiphysis before the age of 6 years 11 months provided additional evidence that growth in stature was by this time coming to an end, while serial measurements of the skull showed that no further increase in circumference had occurred between the ages of 5 years 9 months and 6 years 11 months, as indicated in Table 1. A somewhat similar pattern of skeletal development has been recorded by Greulich and Pyle (1959) in a case of precocious puberty in which the first menstrual period had occurred when the child was 7 months of age (Fig. 3).

Dental Development. Two criteria in common use for the assessment of the maturation of the dentition are tooth emergence and tooth calcification. Adequate norms are not available for the emergence of deciduous teeth nor for the calcification of the permanent dentition of New Zealand children and American standards have consequently been used. Data compiled by Leslie (1951) provide norms for the emergence of permanent teeth of New Zealand children. In Table 3 the number of deciduous teeth which had emerged when the child was 20 and 50 months of age has been compared with the mean number of deciduous teeth present in 'middle class' American girls of comparable ages (Meredith,

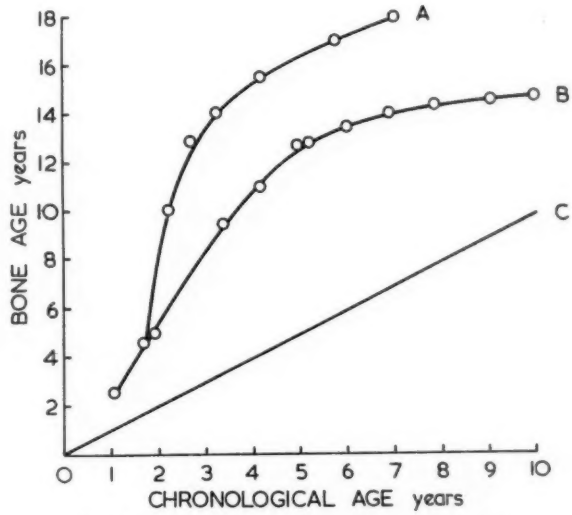


FIG. 3.—Bone age in relation to chronological age:
A—McGeorge and Connor's patient;
B—Greulich's patient;
C—Normal development curve.

TABLE 3

EMERGENCE OF DECIDUOUS AND PERMANENT TEETH: COMPARISON WITH NORMS

Dentition	Child		Norms	
	Chronological Age	No. of Teeth Present	Chronological Age	Mean No. of Teeth Present
Deciduous teeth	20 months	12	*18 months 24 months	12·4 16·4
	50 months	20	*42–53 months	20
Permanent teeth	5 years 9 months 6 years 11 months	4 7	†6 years †7 years	3·78 8·83

* 'Middle-class' American girls (Meredith, 1946). † New Zealand girls (Leslie, 1951).

1946), and the number of permanent teeth present at 5 years 9 months and at 6 years 11 months with the mean number of permanent teeth in groups of New Zealand girls of comparable ages. The dental age reached by the child at each of these latter chronological ages has also been assessed (Table 4) from the extent of formation and calcification of the mandibular left permanent first molar (Gleiser and Hunt, 1955). These data indicate that deciduous and permanent tooth emergence had occurred within normal age limits, while two observations of the formation of the mandibular left permanent first molar show the close relationship between the chronological age and the dental age. The general conclusion is, therefore, that there is nothing remarkable about the rate of development of the dentition in this case.

TABLE 4

DENTAL AGE ASSESSED FROM STAGE OF DEVELOPMENT OF MANDIBULAR LEFT PERMANENT FIRST MOLAR

Chronological Age	Dental Age
5 years 9 months 6 years 11 months	*6 years 1 month *7 years

* Gleiser and Hunt (1955).

Development of Physical Skills

Although an assessment of the child's physical skills had unfortunately not been undertaken during infancy, her mother reported that she had sat up at the age of 8 months, crawled at 10 months and walked without assistance at 18 months. In an analysis of 25 cases of precocity, half of which had reached puberty during the first year of life and the remainder during the second year, Dennis (1941) found that the age at which walking commenced varied from 9 to 18 months, with a mean of 13·58 months, while in a series of 34 cases, Jolly (1955) found that only one child had walked at a significantly early age, the remainder at the normal times.

At the age of 6 years 11 months our patient was referred for assessment to the University of Otago School of Physical Education. Her physical skills in terms of whole body movement were then found to be well ahead of her years, while her control of running, jumping, catching, throwing, aiming and balance were all remarkable for a child of her age. Perhaps her most outstanding skills were speed in running and force in throwing. Girls of all ages have often found difficulty in over-hand throwing, but she could throw a tennis ball over-arm at a target 20 feet away with surprising force and accuracy. It was deduced from a series of over 20 movements in which she was tested, that she was not only skilful for her age, but also for her size. There are as yet no standard norms in such skills in New Zealand, but she was far superior to certain American standards specified as being normal for a child of her age.

On a hand dynamometer she constantly produced a grip of 18 kg. with her right hand and 22 kg. with her left. These figures correspond with the norms of American girls of 10 and 12 years of age respectively (Brooks, 1929; Methency, 1940). The question of handedness was somewhat puzzling, as although she performed most complex skills with her right hand, when asked to do things with her left hand she could do them fairly easily. When she was gripping the dynamometer the upper arm muscles, which are auxiliary to these movements, were noted to be unusually hard. The general impression gained was one of quite extraordinary strength, a characteristic of cases of sexual precocity which has also been commented upon by Dennis (1941) and by Jolly (1955).

Her powers of general relaxation were tested on two occasions by Rathbone's technique and by the Roper technique. Initially, observation of her various movements showed that she was unusually tense. When she was seen again, although the number of residual tensions in her movements had diminished markedly, there still remained some residual habitual tension, probably psychogenic in origin. The child was found to have a good sense of rhythm, and was very quick to pick up quite difficult rhythms from a gramophone record and from drum beats.

Psychological Development

The Longitudinal Picture. The child was first referred to the University of Otago Child Guidance Clinic for assessment of intelligence and general behaviour at 2 years 3 months, when it was tentatively estimated that her mental age was 2 years 11 months, giving an intelligence quotient of 133. On the second visit at 3 years 3 months it was definitely established that the child was of superior intelligence, with an I.Q. of 135 on the

Terman-Merrill Revision of the Stanford-Binet Test. This high rate of mental development continued uniformly over the subsequent observation period of four and a half years, and seemed to be unrelated to her accelerated growth in other respects. Remarkable motor development and co-ordination was noted in the first testing, and this was sustained in subsequent examinations, as is well illustrated by her performance on the Goodenough Draw-a-man Test, where at the age of 5 years 9 months she scored a drawing age of 11 years (Fig. 4). It is also seen in her high ability in free expression drawings (Figs. 5 and 6) and in her remarkably good printing and figuring. On the Minnesota Rate of Manipulation Test she showed very highly developed hand-eye co-ordination and execution in both gross and fine movements, and at the age of 5 years 9 months exceeded the norm for 8-year-olds. Her verbal expression and content were consistent with her mental age and were extremely highly developed on the last test occasion at the age of 6 years 11 months.

On the first three test occasions (ages 2 years 3 months; 3 years 3 months; and 4 years 2 months) she was found to be emotionally stable and socially mature for her age, and no abnormal mental or personality manifestations were detected, although she was slightly withdrawn on the third occasion. On subsequent testings her lack of fluency of personality was further noted; she tended to be serious and lethargic, but responded when stimulated. On the Raven Controlled Projection Test and the Rosenzweig Picture Frustration Tests there were an unusual number of aggressive responses. Some signs of tension appeared during testing, for example, chewing

FIG. 4.—Goodenough Draw-a-man Test: Chronological age 5 years 9 months; performance age 11 years.

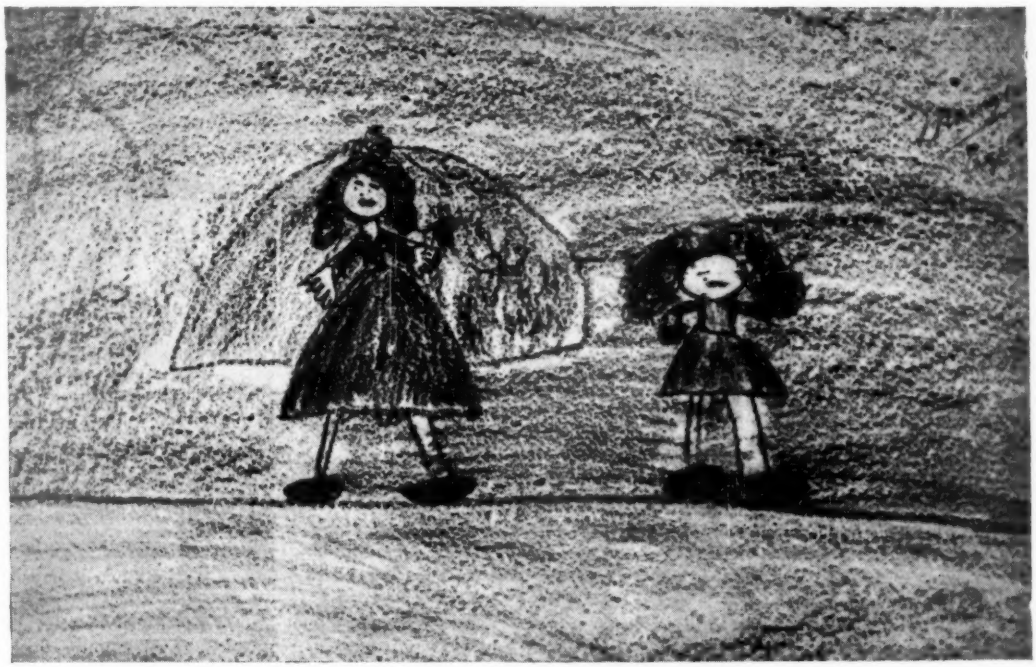


FIG. 5.—Crayon drawing at 5 years 3 months.

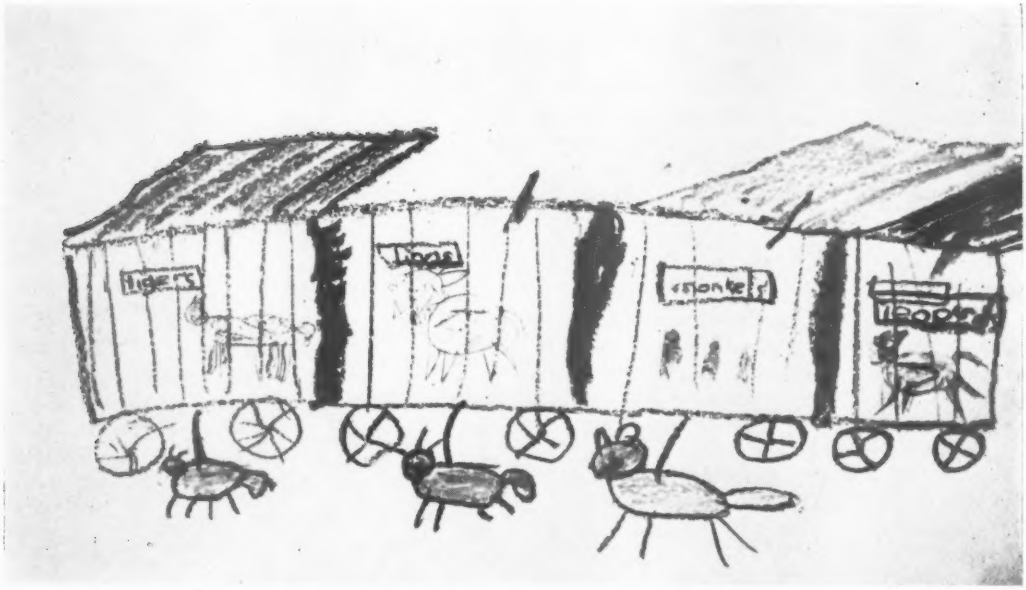


FIG. 6.—'Travelling circus train', drawn at 6 years 11 months.

of fingers and undue preoccupation with manipulating her handkerchief. Most of the above symptoms appeared concurrently with commencing school. Here she was regarded a little differently by the other children, being the centre of attention because of her leadership qualities, and was on one occasion observed showing her breasts to the group. However, the school reports did not record any emotional or social problems in the school setting.

She commenced school at the beginning of 1958 at the age of 4 years 6 months and the teacher considered her ready to start reading immediately. Throughout the first year she was found to be performing at an average level in a bright group in both reading and number work. The only activity in which she then showed more maturity than her fellows was in drawing. Early in 1959, at the age of 5 years 5 months, she was still performing at the average level of a fast-moving group of age range 6 years—6 years 3 months. In the middle of the year her reading age of 6 years 1 month on the Schonell Graded Word Test matched her chronological age and was not testable on the Schonell Simple Prose Test, while her arithmetic age was 6 years 4 months on the Schonell Diagnostic Arithmetic Test. Both these tests indicate that in relation to her mental age she was retarded in these subjects. Her writing and printing were exceptionally good. She was promoted to the standards in the usual way in 1960, and on retesting in the middle of the year at the age of 6 years 11 months her reading age was 9 years 5 months, an increase of 3 years 4 months during the 12-month period. This indicates that she was then performing at the level of her mental age of 9 years 6 months, and was therefore no longer retarded. Her arithmetic age was then 7 years 9 months, indicating some remaining retardation in arithmetic, but this is likely to be remedied as she passes through the standards.

The Present Picture

Appearance and General Impression. At the age of 6 years 10 months the patient has the appearance of a girl much older than she actually is. She is a big, rather tall girl, well proportioned, and has a facial maturity, poise and co-ordination of movement beyond her years. Her general behaviour, including speech content and expression, is very mature for her age, but not more than would be expected of a girl of her intellectual level.

Intellectual Functioning. On the Wechsler Intelligence Scale for Children the patient scored a Full Scale I.Q. of 138, her highest score being on the Information Sub-test. This was confirmed by an I.Q. of 139 on the Terman-Merrill Revision of the Stanford-Binet Test. She is highly endowed verbally, but is not particularly fluent in the person-to-person situation. However, on tests of creativity of ideas and fluency of expression she scored very highly.

School Performance and Adjustment. Her present school performance is in keeping with her intellectual level and she is only slightly retarded in arithmetic. She has remarkable ability in printing and writing, and her executive ability in drawing and art work is outstanding. It seems that, all other circumstances being favourable, she could be accelerated by one standard in the near future.

Relations with the teacher and attitude to school are very good. She is reported, on the Bristol Social Adjustment Guide (Child in School), to be friendly

and willing, to smile readily, to be keen to answer and to appreciate praise. She is also a good mixer, gets on well with those of her own age, is healthily noisy and boisterous in play, but inclined to be placid in school. The teacher reports that she is sometimes moody and fidgets a little, but there are no behaviour problems in the school setting.

Home Life. The patient is the seventh child in a family of eight, living in a rural area. The mother reports that there were no difficulties at birth and that the child passed her milestones of weaning, walking and talking normally and little ahead of the other children. The home background has been warm and affectionate and very stable. The Bristol Social Adjustment Guide (Child in the Family) records that the parent-child and parent-parent relationships are good and that the child is very attached to her siblings and is liked by them. This was confirmed by the Bene-Anthony Family Relations Test, in which no undue ambivalent or egocentric responses were recorded, and the distribution of incoming and outgoing feelings to various members of the family was normal. On Bellak's Children's Apperception Test the interpretations were consistent with a complete absence of tension and maladjustment in the family setting. Only two negative responses were recorded—a fear of animals and shyness with strangers who visit the home. This was noted earlier in her placidity in school and her tenseness and withdrawal symptoms in the earlier clinic sessions.

Emotional and Social Adjustment. As mentioned earlier, the child is considered to be socially mature and emotionally well adjusted, but on the third examination some indications of emotional tension were noted and she was slightly socially withdrawn in the clinic setting. Apart from this, observation and reports indicate that she is adjusting very well both to her sexual precocity and to her home and school setting. She plays equally well with both sexes of her own age, brings companions to her home and visits others. She reacts to punishment in the normal way, and the Rosenzweig Picture-Frustration Test indicates that she characteristically turns her feelings and actions outwardly on to the environment when she is frustrated.

On the 'Day at School' and 'Day at Home' tests she gave an account of the normal activities of a 6-year-old. Her interests and pastimes are those ordinarily indulged in by her friends of similar age. On the 'Myself' test her concept of self does not depart from that of a bright child of her own age group. Her main hobbies are reading, drawing and 'dressing up'.

Attitude to Her Condition. Her attitude to coming to the hospital and to the child guidance clinic is one of apparent acceptance, ostensibly to see how well she can do some 'puzzles' and for a short holiday in the city. The parents have been co-operative, and have played a supportive role in her temporary absences from home, visiting her frequently and giving simple assurances and explanations. They have good insight into the child's needs, an example being their explanation to her of her menstrual periods. They have assured her that the reason for this is that she has developed a little earlier than other girls. They encourage her to use the lavatory on her own during these periods. They have not felt it necessary to give her any direct sex information not appropriate to her age, nor do they draw attention to her condition by overemphasizing it. Her teachers are known to the parents and co-operate fully. Her siblings realize that she is a little different from them for the same reason given to the patient by the parents. The attitude of other children at school is not known, but the teachers have not noticed anything out of the ordinary. It was not thought appropriate to draw direct attention in the clinic to her precocious sexual development in order to get the child's own attitude to her condition. However, in response to the question 'Why do you think we are all trying to help you?' she replied 'So that I will keep well'.

Her mother says the family are particularly fortunate in that they live in a small closely-knit rural community and that therefore they can both preclude and remedy any undesirable attitudes towards the child's unusual condition.

Discussion

Diagnosis. The diagnosis of so-called 'constitutional' precocity rests upon the occurrence of premature but orderly sexual maturation, together with the absence of any evidence pointing to an organic basis for the abnormality. In the present case, although no relevant physical signs were detected, consideration was given to the possibility of a granulosa tumour of the ovary, and an exploratory laparotomy was accordingly performed. This step was apparently unnecessary, since granulosa tumours are exceedingly rare, particularly in childhood, and in children have always been palpable by the time symptoms are apparent (Jolly, 1955). It has therefore been recommended (Novak, 1944; Gross, 1953) that laparotomy should be performed only if there is a palpable mass, the absence of which should be confirmed by bimanual examination under anaesthesia. Jolly makes the further point that when a mass is palpable only under an anaesthetic it is usually found to be a follicular cyst of one ovary, a not uncommon condition in children with precocious puberty.

Relative Degrees of Precocity Occurring in Various Systems. In normally developing children there is a close relationship between sexual maturity on the one hand and skeletal maturity and the adolescent growth spurt on the other (Shuttleworth, 1938a; Buehl and Pyle, 1942; Simmons and Greulich, 1943). A girl who develops her secondary sex characters early has her adolescent height spurt early, reaches 90% of her mature height early and undergoes the changes in ossification of her hand,

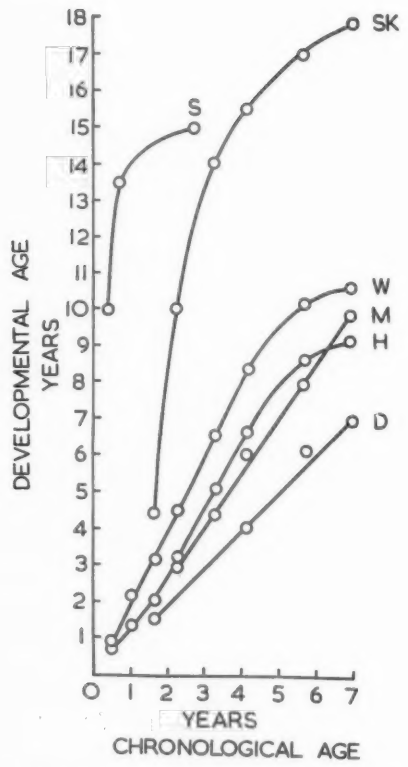


FIG. 7.—Composite development chart. The age at which child passed various developmental milestones (chronological age) has been plotted against the average age at which normal children pass corresponding milestones (developmental age). The dental age curve approximates closely to the curve of average normal development for all systems. For sources of norms, see text.
S: sex age; SK: skeletal age; W: weight age;
H: height age; D: dental age.

wrist and knee early (Tanner, 1955). This normal association continues to be manifest in cases of sexual precocity. Among the tissues more or less responsive in the hypothalamic group to the stimulation of growth hormone, gonadotropins and androgens or oestrogens, and in the adrenogenital group to the stimulation of androgens, the following order of decreasing responsiveness was established (Seckel, 1950): gonads (in the hypothalamic group only), non-gonadal primary genitalia, secondary sex characteristics, skeletal epiphyses, body and organ masses and metaphyses of long bones. Two tissues, on the other hand, the teeth and the central nervous system, responded little or not at all to the 'hormonal crisis' of sexual precocity. These developmental patterns have been illustrated by Seckel by means of biological growth charts based upon detailed study of three cases of hypothalamic precocity, and one case of adrenogenic virilism.

A chart of similar type (Fig. 7) has been constructed to illustrate the various developmental patterns shown by our own patient. In this the chronological ages at which the child passed various developmental milestones have been plotted against the average ages at which the corresponding milestones are generally passed by normal children. From these curves it is evident that the effects of the precocious stimulant upon various anatomical and physiological systems have differed considerably in both extent and rate. As in Seckel's cases, the most marked degree of precocity occurred in relation to sexual development, followed in descending order by skeletal development, weight and height increments. Throughout the period of observation mental development proceeded at a uniform rate slightly above average, while the eruption and calcification of the teeth were normal for age.

Tanner (1955) has pointed out that there is some general factor of bodily maturity, creating a tendency for a child to be advanced or retarded as a whole, but that within this there are set groups of more limited maturities which vary independently of each other. Thus the correlations between dental and skeletal development, and between intelligence test score and reproductive maturity, though positive, are both low. Further, in precocious puberty there is advancement of genital and skeletal maturity without any corresponding effect upon the teeth (Taft, 1941; Seckel, 1950; Jolly, 1955; Resch, 1958). These observations do not support the statement of Schour and Massler (1943) that in precocious puberty the apposition of enamel and dentine is accelerated, but not to the same degree as is skeletal growth.

The failure of the dental tissues to respond to the same extent as other tissues in precocious puberty has promoted several explanations of the phenomenon. One explanation that has received wide notice is that 'the most intensive development of teeth occurs prior to the onset of the endocrine stimulation which, by hypothesis, is responsible for the timing of the menarche and of patterns of growth in all other available measurements. The period of most active eruption of permanent teeth is from $9\frac{1}{2}$ to $10\frac{1}{2}$ years, whereas the period of most active growth in other available measurements occurs approximately two years later' (Shuttleworth, 1938b). Tooth development, however, includes actual formation, movement within bone before eruption and clinical emergence into the mouth. Kraus (1959) has placed initial calcification of the deciduous dentition as early as 12 weeks *in utero*. Formation of the permanent third molars continues until adulthood. Thus there is ample opportunity for hormonal influence on the dentition in precocious

puberty. But for some inexplicable reason the dental tissues do not seem to be affected.

Psycho-sexual Precocity. Most reports of precocious sexual development deal mainly with the somatic aspects of the cases, but in more recent studies psychological reports are available. Keene and Stone (1937) in their review of 80 cases, reported that only 15 patients were tested for intelligence, and that the mental development of these was somewhat below the average. Other workers (Leiner, 1920; Gesell, Thoms, Hartman and Thompson, 1939; Seckel, 1950; Jolly, 1955) have also reported average intelligence, and use this as evidence that mental growth is not affected by the sexual precocity. As Gesell puts it, there is 'a preferential immunity of the central nervous system to certain forms of endocrine imbalance'. The high level of intelligence in the present case is not inconsistent with this latter hypothesis, but further longitudinal and cross-sectional studies of the mental development of these patients are necessary to confirm it.

When we turn to other aspects of psychological development which are more directly environmentally conditioned, we see that the patient under consideration is no more mature socially and emotionally than her high level of intelligence would warrant, and that she is 'child-like' with regard to psycho-sexual development. In the studies of Hampson and Money (1955) and of Jolly (1955) it is concluded that there is little relationship between psycho-sexual maturity and constitutional precocious bodily development of the kind we are dealing with here. Tanner also claims that behaviour is unaffected by the stimulus of glandular secretion, and that children with precocious puberty seldom show signs of heterosexual activity. An interesting study by Rafferty and Stein (1958) of the effect of early menarche on ego-development states that the evidence for heterosexual drive being increased is not great, but it is not easy to demonstrate this conclusively, since psychological maturation is complexly determined. While our own case largely confirms the above hypothesis, it is difficult to discriminate between precocious behaviour due to general constitutional factors and that due to accelerated psychological growth. We must wait upon further studies of the growth curves of such children and more precise studies of their psychological behaviour and personality development along the lines suggested by the work of Rafferty and Stein.

Guidance and Management. Idiopathic or constitutional sexual precocity is due to the precocious secretion of pituitary gonadotropins, and no method of preventing this is at present available. Consequently the statement made by Morse in 1897 that 'The medical treatment of this condition is absolute abstinence from all therapeutic measures. The psychological treatment, however, is important' remains equally true today. Money, Hampson and Hampson (1957) have formulated a valuable guide to the psychological and social management of these cases. In summary they state that the psychological development of these children resembles in manner and speed that of their somatically normal siblings, and correlates with the variety of life experiences encountered and transacted. Sexually precocious children are capable of regulating their sexual conduct as well or as badly as normal adolescents. Dependent on general social experience, sexually precocious children may or may not be precocious in social maturation, but seem to benefit from association with children closer to them in body maturity than in chronological age. It is safe and desirable to speed up school entrance and progress, provided the degree of acceleration is consonant with I.Q. rating, and provided there is some individual instruction and coaching. Care must be taken not to forget or disregard the chronological age of the sexually precocious child, and to avoid setting standards and expectations of performance to which the child cannot conform. In the case at present under consideration the child has been particularly fortunate in that parents, school and social setting all provide optimum conditions for sound development.

Summary

A detailed study has been made of the first seven years of the life of a child in whom the initial signs of sexual development were observed at the age of 5 months and the first menstrual period occurred at 9 months. The diagnosis of 'constitutional' precocious puberty was based upon the occurrence of premature but orderly sexual maturation, together with the absence of any evidence pointing to an organic lesion. Exploratory laparotomy at the age of 27 months demonstrated normal ovarian tissue with a recent corpus luteum.

Weight and height charts were available from birth, while subsequent physical and mental development was assessed on six occasions between the ages of 1 year 8 months and 6 years 11 months. Studies included somatic measurements, dental examinations, skeletal and dental radiographs, the features of sexual development, an assessment of physical skills, psychometric tests, and detailed investigation

of emotional and social adjustment at home and at school.

As has been previously observed, the effects of the precocious stimulant upon various anatomical and physiological systems differed considerably in both extent and rate. The most marked degree of precocity occurred in relation to sexual development, followed in descending order by skeletal development and weight and height increments. Mental development proceeded at a uniform rate slightly above average and appeared to be uninfluenced by other factors, while the eruption and calcification of the teeth were normal for age. The child was no more mature socially and emotionally than her high level of intelligence warranted, while psycho-sexual development showed no precocity.

Cases of this type require no active medical treatment, but psychological guidance should be available to the patient, the parents and the teachers in order that the various agencies may be co-ordinated to promote the child's optimum adjustment. If reasonable care is taken in these matters there is no reason why the psychological prognosis should not be as good as the medical.

Our thanks are due to Associate Professor J. E. Caughey, who referred the child to the Paediatric Department; to Professor J. L. Wright for reports on pelvic examinations and laparotomy; to Dr. F. Desmond for the histological report on ovarian biopsy tissue; to Dr. A. C. Begg for serial radiological determinations of the bone age; to Mr. M. R. Kean for reports on the dentition; to Associate Professor P. A. Smithells for assessment of physical skills; and to Dr. R. Seddon for the initial intellectual assessment of the child. Details of development during the first 18 months were obtained from the records of the Plunket Society. Illustrations were prepared by the Department of Medical Photography.

References

Brooks, F. D. (1929). *The Psychology of Adolescence*. Houghton Mifflin, Boston.

Buehl, C. C. and Pyle, S. I. (1942). The use of age at first appearance of three ossification centers in determining the skeletal status of children. *J. Pediat.*, **21**, 335.

Dennis, W. (1941). Effect of pubertas praecox on the age at which onset of walking occurs. *Amer. J. Dis. Child.*, **61**, 951.

Flecker, H. (1942). Time of appearance and fusion of ossification centers as observed by roentgenographic methods. *Amer. J. Roentgenol.*, **47**, 97.

Gesell, A., Thoms, H., Hartman, F. B. and Thompson, H. (1939). Mental and physical growth in pubertas praecox; report of fifteen years' study of a case. *Arch. Neurol. Psychiat.* (*Chicago*), **41**, 755.

Gleiser, I. and Hunt, E. E., Jr. (1955). The permanent mandibular first molar: its calcification, eruption and decay. *Amer. J. phys. Anthrop.*, **13**, 253.

Gray, H. (1935). *Anatomy, Descriptive and Applied*, 26th ed. Ed. T. B. Johnston. Longmans, Green, London.

Greulich, W. W. and Pyle, S. I. (1959). *Radiographic Atlas of Skeletal Development of the Hand and Wrist*, 2nd ed., p. 2. Stanford University Press, Stanford, California.

Gross, R. E. (1953). *The Surgery of Infancy and Childhood*, p. 501. Saunders, Philadelphia.

Hampson, J. G. and Money, J. (1955). Idiopathic sexual precocity in the female; report of three cases. *Psychosom. Med.*, **17**, 16

Jacobsen, A. W. and Macklin, M. T. (1952). Hereditary sexual precocity: report of a family with 27 affected members. *Pediatrics*, **9**, 682.

Jolly, H. (1955). *Sexual Precocity*, pp. 8-22. Thomas, Springfield, Illinois.

Keene, C. M. and Stone, C. P. (1937). Mental status as related to puberty praecox. *Psychol. Bull.*, **34**, 123.

Kraus, B. S. (1959). Calcification of the human deciduous teeth. *J. Amer. dent. Ass.*, **59**, 1128.

Leiner, J. H. (1920). Pubertas precox with especial attention to mentality. *Endocrinology*, **4**, 369.

Leslie, G. H. (1951). *A Biometrical Study of the Eruption of the Permanent Dentition of New Zealand Children*, p. 26. Government Printer, Wellington.

Lloyd, C. W., Lobotsky, J. and Morley, M. (1950). Precocious puberty. *Pediatrics*, **6**, 343.

Meredith, H. V. (1946). Order and age of eruption for the deciduous dentition. *J. dent. Res.*, **25**, 43.

Methency, E. (1940). *University of Iowa Studies in Child Welfare*, Vol. 17, No. 2. Quoted by Munrow (1955).

Money, J., Hampson, J. G. and Hampson, J. (1957). Quoted by Wilkins (1957).

Morse, J. L. (1897). Precocious maturity. *Arch. Pediat.*, **14**, 241. Quoted by Jolly (1955).

Munrow, A. D. (1955). *Pure and Applied Gymnastics*, p. 85. Arnold, London.

New Zealand Department of Health (1956). A preliminary report on the 1954 survey of heights and weights of New Zealand primary school children. *Annual Report of the Director-General of Health. Appendix III.* Government Printer, Wellington.

Novak, E. (1944). Constitutional type of female precocious puberty, with report of nine cases. *Amer. J. Obstet. Gynec.*, **47**, 20.

Rafferty, F. T. and Stein, E. S. (1958). A study of the relationship of early menarche to ego development. *Amer. J. Orthopsychiat.*, **28**, 170.

Resch, C. A. (1958). Clinically observed oral manifestations of endocrinopathy. *Dent. Clin. N. Amer.*, July, p. 397.

Rush, H. P., Bilderback, J. B., Slocum, D. and Rogers, A. (1937). Pubertas praecox (macrogenitosomia). *Endocrinology*, **21**, 404.

Schour, I. and Massler, M. (1943). Endocrines and dentistry. *J. Amer. dent. Ass.*, **30**, 763.

Seckel, H. P. G. (1946). Precocious sexual development in children. *Med. Clin. N. Amer.*, **30**, 183.

—— (1950). Six examples of precocious sexual development: II. Studies in growth and maturation. *Amer. J. Dis. Child.*, **79**, 278.

Shuttleworth, F. K. (1938a). *The Adolescent Period: A Graphic and Pictorial Atlas. Monogr. Soc. Res. Child Developm.*, **3**, No. 3. Quoted by Seckel (1950).

—— (1938b). *Sexual Maturation and the Skeletal Growth of Girls Age Six to Nineteen. Ibid.*, **3**, No. 5. Also quoted by Seckel.

Simmons, K. and Greulich, W. W. (1943). Menarcheal age and the height, weight and skeletal age of girls age 7 to 17 years. *J. Pediat.*, **22**, 518.

Stuart, H. C. and Stevenson, S. S. (1959). In *Textbook of Pediatrics*, ed. W. E. Nelson, 7th ed., p. 50. Saunders, Philadelphia.

Taft, L. L. (1941). Dental findings in five-year old Peruvian mother. *N.Y. J. Dent.*, **11**, 225.

Talbot, N. B., Sobel, E. H., McArthur, J. W. and Crawford, J. D. (1952). *Functional Endocrinology from Birth through Adolescence*, ch. 5, The Ovaries. Harvard University Press, Cambridge, Mass.

Tanner, J. M. (1955). *Growth at Adolescence*, pp. 56-63. Blackwell, Oxford.

Wilkins, L. (1957). *The Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence*, 2nd ed., ch. 11, p. 198, Precocious Sexual Development. Thomas, Springfield, Illinois; Blackwell, Oxford.

THE POSTNATAL DEVELOPMENT OF ALVEOLI IN PREMATURE INFANTS

BY

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The general gross features of development of the alveoli of the lung in the foetus are well known and are described in the textbooks on paediatric pathology (Morison, 1952; Potter, 1952). The classical description of the development of the lung divides its growth into three phases, bronchial, tubular and alveolar, of which the latter takes place last and chiefly after birth. This late alveolar growth was thought to be due largely to the stimulus of breathing (Dubreuil, Lacoste and Raymond, 1936). However, Laumonier (1952) and Lelong and Laumonier (1953) from subjective assessment of the lungs of infants born prematurely, found no evidence of precocious development of the lungs in 'prem' infants and suggested that the growth of the lung was determined by maturity alone.

In order to elucidate some of these problems we have attempted to put some aspects of lung development on an objective and measurable basis (Emery and Mithal, 1960) and have shown that the peripheral respiratory unit has a radial count of about two alveoli at 28 weeks and up to four at 40 weeks gestation age. The present study uses this measurement to compare the alveolar count in children born prematurely who survived for varying lengths of time over 17 days, with the alveolar counts that the same children would have had, had growth continued *in utero*.

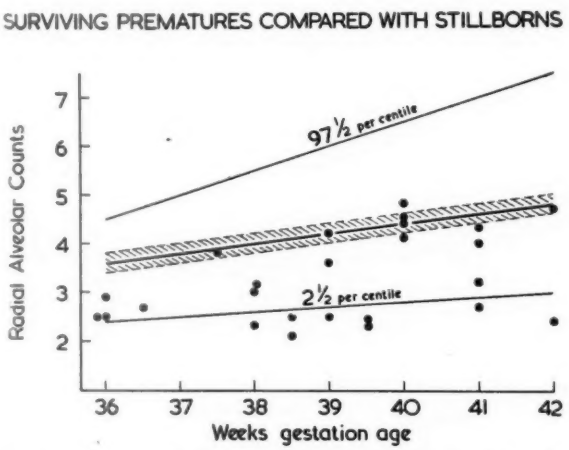

FIG. 1.—A chart showing the radial alveolar counts related to gestation age. The mean line and shaded area and the 2½ percentile and 97½ percentile are from normal stillborns. The black spots represent the counts from children born prematurely and surviving for varying periods beyond seven days.

Material and Methods

Lung sections from babies born at less than 38 weeks' gestation were surveyed. All those in which there were congenital anomalies of any system and those with gross pulmonary pathology were excluded.

Ten radial counts were made from each case, using the same method as used for establishing normal counts (Emery and Mithal, 1960). To make assessment less biased, lung sections from full-term infants were also included when counting was done. At the time of counting, only the serial autopsy number was known, and no clinical data were available.

From those data, only those cases were selected that had lived for at least one week after birth as only these could be expected to show any maturation changes. Twenty-five such prematurely born infants were thus found suitable for analysis.

The average radial alveolar count from each case was then plotted and related to the gestation age at the time of death. Thus an infant born at 30 weeks gestation age who had lived for six weeks after birth was plotted at 36 weeks gestation age. The graph so obtained was analysed statistically and then superimposed on the chart showing the 2½ and 97½ percentile ranges of stillborns studied previously (Fig. 1).

Statistical analysis was done to test the difference between the means of the liveborn and stillborn groups (Student's 't' test). The formula for 't' tests is:

Difference between means/Standard error of difference between means.

The standard error of difference between means is calculated by the formula $\frac{\sigma 1^2}{n_1} + \frac{\sigma 2^2}{n_2}$.

The 't' value obtained was compared with the 't' value for the number of cases $(n_1 - 1) + (n_2 - 1)$ that is, 59 cases.

Results

The 36 stillborns showed a mean radial alveolar count of 4·211 ($\sigma = 0{\cdot}522$) and the 25 premature born of similar gestation a mean radial alveolar count of 3·264 ($\sigma = 0{\cdot}874$). The difference between the means was 0·947 and the 't' value obtained 4·85, the 't' ratio for tables from 59 cases at 0·001 level being 3·551.

Thus, as shown statistically, the number of alveoli in radial counts from a terminal bronchiole is significantly lower in children born and living over a week after birth than in stillborns of comparable gestational ages.

Discussion

Contrary to the view that birth itself stimulates the growth of alveoli (Dubreuil *et al.*, 1936) we have conclusive evidence that premature birth is associated with a diminished rate of proliferation of alveoli. The diminishing growth may, however, be part of a general diminution in growth associated with factors causing death in these infants. We have reason to believe that this is not entirely the case. The technique applied here, that of comparing measurements of organs of equal gestation age born at different times was used on the growth of the ventricles of the heart. That study showed (in the same cases as were used in the present investigation) no diminution in growth of the right ventricle and actual hypertrophy of the left ventricle after premature birth (Mithal and Emery, 1961). Thus we feel that the relative as well as absolute diminution in growth rate of the lung alveoli found in the present study is valid.

The literature on the lungs of the newborn has largely been concerned with hyaline membrane, atelectasis and infection, but recently Wilson and Mikity (1960) described the post-mortem appearance of lungs of premature infants who showed late respiratory distress, and found instances of thickened inter-alveolar septa which they thought similar to Hamman-Rich syndrome (Hamman and Rich, 1944). Those (Wilson and Mikity, 1960) lungs are a little like the lungs that MacMahon (1948) described as alveolar dysplasia. That lung picture, however, is one that many of us see not infrequently, and we agree with Potter (Potter, 1948) that it does not represent a specific disease. It seems likely that these lungs (Wilson and Mikity, 1960) could well be the result of a diminished alveolar proliferation in immature infants.

Summary

Radial alveolar counts of the terminal respiratory units from 25 infants born prematurely and surviving for over a week were compared with the counts from stillborns of the same gestation age.

After premature birth, there is a significant diminution in alveolar proliferation of the terminal respiratory unit.

Some of the autopsies reported in this study were carried out by courtesy of Dr. A. J. M. Warrack.

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References

Dubreuil, G., Lacoste, A. and Raymond, R. (1936). Observations sur le développement du poumon humain. *Bull. Histol. Tech. micr.*, **13**, 235.

Emery, J. L. and Mithal, A. (1960). The number of alveoli in the terminal respiratory unit of man during late intrauterine life and childhood. *Arch. Dis. Childh.*, **35**, 544.

Hamman, L. and Rich, A. R. (1944). Acute diffuse interstitial fibrosis of lungs. *Bull. Johns Hopk. Hosp.*, **74**, 117.

Laumonier, R. (1952). Remarques sur la structure pulmonaire des prématurés. *Sem. Hôp. (Paris)*, **28**, 2047.

Lelong, M. and Laumonier, R. (1953). Histological and histochemical evolution of the foetal lung; its relation to anoxia in premature infants. In *Anoxia of the New-born Infant*, a symposium organized by the Council for International Organizations of Medical Sciences (Unesco and W.H.O.). Ed. J. F. Delafresnaye and T. E. Oppé p. 61. Blackwell Scientific Publications, Oxford.

MacMahon, H. E. (1948). Congenital alveolar dysplasia. A developmental anomaly involving pulmonary alveoli. *Pediatrics*, **2**, 43.

Mithal, A. and Emery, J. L. (1961). The influence of birth on the weights of right and left cardiac ventricles in prematurely born infants. *Acta paediat. (Uppsala)* **50**, 228.

Morison, J. E. (1952). *Foetal and Neonatal Pathology*, p. 126. Butterworth, London.

Potter, E. L. (1948). Congenital alveolar dysplasia of the lungs. *Pediatrics*, **2**, 507.

—— (1952). *Pathology of the Fetus and the Newborn*, p. 236. The Yearbook Publishers, Chicago.

Wilson, M. G. and Mikity, V. G. (1960). A new form of respiratory disease in premature infants. *Amer. J. Dis. Child.*, **99**, 489.

VOMITING IN THE EARLY DAYS OF LIFE

BY

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'How difficult it often is to appraise exactly the significance of vomiting in infancy . . .! How much and how little it may mean.'

George Frederic Still

Vomiting in the days following birth is common. Emphasis in the literature is focused on vomiting due to acute alimentary obstruction. Nevertheless, the occasions when vomiting gives rise to anxiety at this age are relatively rare. In the newly-born it is associated with other alimentary conditions not involving obstruction and with a variety of parenteral conditions. This contribution is based upon a clinical study of vomiting in the early days of life with particular reference to the circumstances in which it takes place.

Method of Study

Babies included in the study were observed in the Leeds Maternity Hospital, during the period January 1954 to June 1960 (inclusive). Two series of babies were studied.

Series A consists of healthy infants in whom the occurrence of an isolated or occasional vomit would not, in the normal course of events, have prompted a request for medical aid by the midwife. Series B consists of ailing infants referred for a medical opinion, either solely on account of vomiting, or on account of several clinical signs including vomiting.

Recording of the occurrence of vomiting was dependent upon observations made by labour and lying-in ward sisters and to a lesser extent by mothers. The standards of clinical observation varied considerably. Study of healthy babies was therefore concentrated in one lying-in ward, in which recorded observations were agreed jointly by the ward sister and the resident paediatric senior house officer. All babies in whom vomiting was a feature were automatically transferred from the labour or lying-in ward to the special baby unit in accordance with established routine. Clinical observations on these babies were discussed daily by midwives and resident and visiting medical staff. For the purposes of the study no attempt has been made to differentiate vomiting from regurgitation.

Clinical Observations

Series A: Healthy Babies (273). The series consisted of 141 males and 132 females, all of whom were born in the Leeds Maternity Hospital. Vomiting in the first week of life was noted in 177 (65%) of the series; commenced within 72 hours of birth in two-thirds of the babies, and rarely persisted for more than two days. Mucus was a feature of the vomitus in 17 cases.

Series B: Ailing Babies (498). Of the 498 babies in the series, 464 were born in the Leeds Maternity Hospital, 11 in nursing homes and 23 in their own homes. There were 260 males and 238 females.

The gestation periods and the methods of delivery in the two series are compared in Table 1. Forty-five babies in Series B died within four weeks of birth. The causes of death are given in Table 2.

TABLE 1

SERIES A AND B: GESTATION PERIODS AND METHODS OF DELIVERY COMPARED

	Series		Series	
	A (No.)	B (No.)	A (%)	B (%)
Gestation Period:				
<38 weeks ..	26	109	10	22
38—42 weeks ..	216	316	78	63
>42 weeks ..	31	73	11	15
Delivery:				
Normal	232	277	86	56
Instrumental ..	23	132	9	26
Caesarean section	18	89	5	18

Reasons Prompting Comment on Vomiting

The reasons prompting the midwife to draw special attention to the occurrence of vomiting were varied and are summarized in Table 3.

TABLE 2

CAUSES OF DEATHS OCCURRING UNDER THE AGE OF 4 WEEKS (45 INFANTS)

Cause	Number of Infants
Infection:	
Septicaemia	2
Septicaemia with meningitis	4
Pneumonia	2
Acute abdominal obstruction:	
Atresia	7
Volvulus: mesenteric bands	1
Hirschsprung's disease	1
Meconium ileus	3
Other congenital anomalies:	
Cardio-vascular	6
Neurological	8
Biliary atresia	1
Miscellaneous:	
Duodenal ulcers	2
Cold injury	2
Hyaline membrane	4
Suprarenal haemorrhage	1
Kernikterus	1

TABLE 3

CHARACTERISTICS OF VOMITING/VOMITUS PROMPTING FIRST REPORT BY MIDWIFE (498 INFANTS)

Characteristic	Number of Infants
Vomiting:	
Persistence, regardless of severity	74
Forcefulness/violence	50
Association with failure to progress	19
Complication of known illness	267
Vomitus:	
Abnormal colour	79
Notably bulky	9

TABLE 4

CLINICAL CONDITIONS WITH WHICH VOMITING WAS ASSOCIATED (498 INFANTS)

Clinical Condition	Number of Infants
Gastro-enteral:	
Difficulties in feeding management	113*
Gastric disturbance by known irritant	37
Pylorospasm	43
Alimentary obstruction:	
pyloric stenosis	4
acute	17
Alimentary infection	7
Parenteral:	
Infection	29
Developmental anomalies	23
Stress of labour or/and delivery	168
Unexplained convulsions	2
Metabolic disorders	11
Cardio-respiratory syndrome	4
Hypothermia/cold injury	13
Haemolytic disease	19
Prematurity (uncomplicated)	8

* Includes four infants with hiatus hernia.

In slightly over 50% of the babies initial concern arose from the possible influence on prognosis of vomiting occurring in the presence of trauma, infection, a congenital anomaly or metabolic disturbance. Otherwise unusual coloration of the vomitus and persistence regardless of severity were the most common sources of disquiet. It was exceptional for there to be visible evidences of dehydration even in infants failing to progress. Anxiety concerning unsatisfactory progress usually arose from failure of an infant to gain weight and only rarely from pronounced loss of weight.

Clinical Findings with which Vomiting was Associated

Clinical conditions with which vomiting was associated are grouped in Table 4 according as they were gastro-enteral or parenteral in origin.

Difficulties in Feeding Management. These accounted for the vomiting in 113 babies. The swallowing of wind in excessive amounts was of major importance in the presence of palatal defects, buccal deformities, nasal obstruction due to rhinorrhoea, choanal atresia and other causes, delay in the functional co-ordination of breathing and swallowing, and abnormalities of the mother's breasts or nipples. Wind swallowing was a feature also in 24 babies in whom vomiting was attributable to insufficiency of the mother's breast secretion. The vomiting in these infants usually ceased when complementary bottle feeds of banked human milk were given. In the case of 16 of these infants complete breast feeding was eventually successfully established. There was no instance of a recurrence of vomiting.

Bottle feeds of excessive bulk accounted for vomiting in four premature babies and in one infant born at term.

'Forced feeding' as a cause of vomiting was limited to a small group of babies having in common reluctance to feed, inertia, faint peri-oral cyanosis, coating of the tongue and a dyspeptic facies. This situation was encountered most commonly in babies delivered by caesarean section regardless of the estimated gestation period. Reluctance to feed persisted for four or five days. Vomitus and the results of gastric lavage contained mucus in considerable amounts. In a number of these babies there was delay in the initial evacuation of the bowels, and vomiting appeared to cease soon after the first passage of meconium.

The replacement of human by cow's milk was accompanied by vomiting in 13 babies, the change being effected too rapidly in eight and the first

cow's milk feeds being too strong in five cases. Sensitization to cow's milk was not encountered.

Gastric Disturbance Due to a Known Irritant. Vomiting in 37 babies was stimulated by the presence in the stomach of blood, abnormal fluid or abnormal secretions. Blood was vomited in copious amounts in two cases of duodenal ulcers and in variable amounts in 17 cases of haemorrhagic disease. Other sources of blood included four of congested post-nasal mucosa, two of palatal ulcers and four of fissures of the mother's nipples. Observations made during delivery and on the nature of the vomitus justified ascribing the vomiting of eight infants to swallowed liquor amnii, meconium, or blood or secretions from the maternal birth passages. Minimal blood staining of the vomitus noted on isolated occasions in two babies with haemolytic disease, and in one with pyloric stenosis was regarded as the result rather than the cause of vomiting.

Pylorospasm. Pylorospasm as evidenced by forceful vomiting, vomitus containing a considerable amount of mucus, visible peristalsis and a palpable contractile thickening (as distinct from tumour) of the pylorus, was a feature of 43 cases. The presence of mucus in unusual amounts may have been due to irritation by blood or meconium in the stomach in several of the babies. In general, however, the impression gained was that the mucus was the irritant giving rise to vomiting.

Alimentary Obstruction. Vomiting in four babies was due to pyloric stenosis confirmed at operation in each instance. There were nine examples of complete atresia of the intestines, three of meconium ileus, two of anal atresia and one each of volvulus due to mesenteric bands, partial atresia of the small intestine and Hirschsprung's disease.

Alimentary Infection. Slight vomiting occurred in six babies with frequent loose stools containing a considerable amount of mucus, and causing severe peri-anal excoriation and dehydration. Bacteriological investigations were consistently negative. The intestinal symptoms were considered to be due to viral infection as they occurred at times when adults in the hospital were suffering from influenzal-type conditions. There was one example of vomiting in association with extensive monilial infection of the bucco-pharynx and oesophagus.

Parenteral Conditions

(*a*) *Infection.* Vomiting was a feature in five babies with acute pyelonephritis, in 11 with septicaemia and in seven with acute descending respiratory infections. Urinary infection was coliform in each case. Septicaemia was due to *Meningococcus* in one, *Streptococcus pyogenes* in two, *Staphylococcus pyogenes* in two, and *Esch. coli* in six babies. Meningitis was a feature of the septicaemia in four infants, and was followed by hydrocephalus in two surviving babies. The respiratory infections were staphylococcal in five, pneumococcal in one and coliform in one. Vomiting in six other babies with severe staphylococcal infections (osteomyelitis, parotitis, cellulitis) ceased when oral antibiotic therapy was discontinued.

(*b*) *Developmental Anomalies.* Vomiting was observed in 13 infants with congenital heart disease; nine with hydrocephalus in association with uninfected spina bifida; and in one with unilateral renal agenesis in association with an anomaly of the bladder.

(*c*) *Stress of Labour and/or Delivery.* There was evidence of abnormal stress arising from labour and/or delivery in 168 of the 498 babies in Series B. An interval in excess of three minutes elapsed between the time of delivery and the onset of respiration in the case of 121 infants. Clinical signs of severe asphyxia were a feature of 54 of the infants of whom 15 subsequently developed signs of severe intracranial irritation. Twenty-four other infants showed evidence of intracranial irritation in the absence of preceding signs of post-natal asphyxia. Intracranial birth injury was complicated in three babies by a persistent subdural effusion.

Foetal distress as indicated by abnormal foetal heart action and/or the passage of meconium during delivery of infants delivered by the vertex was recorded in connexion with 51 of the 168 babies in this group. Foetal distress without subsequent neonatal asphyxia or intracranial disturbance was the only clinical finding associated with postnatal vomiting in 23 infants.

Delivery was normal in 48, instrumental in 66 and operative in 54 instances. The estimated gestation period was less than 38 weeks, and 42 weeks or over in the case of 31 and 38 babies respectively: and between 38 and 42 weeks in the case of 99 infants.

(*d*) *Unexplained Convulsions.* Vomiting synchronized with the occurrence of unexplained isolated convulsions in two babies, whose subsequent progress was uneventful.

(*e*) *Metabolic Disorders.* These included infants with galactosaemia (two), tetany (one) and biliary atresia (one), and seven babies born to mothers with diabetes mellitus.

(*f*) *Cardio-respiratory Syndrome.* Four babies with clinical and post-mortem evidence of this

syndrome vomited at irregular intervals during the period of most acute respiratory distress.

(*g*) *Hypothermia*. Admissions from district included 13 infants in whom vomiting was an incidental accompaniment of 'cold injury' characterized by sustained hypothermia, extensive induration of the skin and subcutaneous tissues, anorexia, inertia and albuminuria.

(*h*) *Haemolytic Disease*. Vomiting occurred in a proportion of babies with haemolytic disease at the time of, or shortly after exchange transfusion. This was noted in connexion with 13 infants. In the case of exchange transfusions given on the first day of life, the vomitus consisted solely of mucus and vomiting was accompanied by abdominal distension. Isolated vomiting events occurred also in six infants with jaundice due to haemolytic disease not requiring exchange transfusion.

(*i*) *Prematurity*. Recurrent vomiting at irregular intervals was a feature of eight small disproportionately frail premature infants in whom there was no evidence of disturbed health.

(*j*) *Anaesthetics and Analgesics administered to the Mother*. Inadequacy of records precluded study.

Particulars Concerning Vomiting

The pattern of vomiting varied to some extent according to the nature of the associated clinical findings.

Time of Onset. With remarkable constancy vomiting associated with gastric irritation and the stress of labour and delivery commenced within 48 and usually within 36 hours of birth. Babies with subdural effusions provided an exception, the age at the commencement of vomiting varying from 6 to 16 days. The average age at onset of vomiting due to pyloric stenosis was 10 days, the youngest being 5 days. Corresponding ages for pylorospasm were 3 days and 1 day. Vomiting due to acute intestinal obstruction commenced one to six days after delivery, delayed onset being associated with low obstruction. In the infants with hiatus hernia vomiting started in the second week of life.

Delayed onset of vomiting was most constant when attributable to infection, the average age being 9 days, and the range 1 to 14. The day of onset in babies with hydrocephalus varied from the first to the fourth and in those with congenital heart disease from the first to the eleventh. When occurring in association with 'cold injury' the commencement of vomiting was related to the time of development of hypothermia and ranged from 1 to 17 days of age, averaging 3 days. There was variation also in the age at which vomiting, explained by difficulties in feeding management, started. The youngest baby was aged 1 day and the oldest 13 days, the average age being 5 days.

Duration. Vomiting related to exchange transfusions rarely persisted more than a few hours. The rapidity with which vomiting ceased in babies with gastric irritation was dependent upon the effectiveness with which irritant material was removed. On an average, vomiting terminated within four days. Vomiting associated with pylorospasm persisted on an average for seven days, but with diminishing severity and frequency, with the commencement of gastric lavage. In no case did vomiting due to hiatus hernia cease in less than four weeks. Persistence was a feature also of vomiting occurring in the presence of severe infection. In babies surviving infection, the average duration of vomiting was two weeks and the longest eight. Aspiration of subdural effusions resulted in the cessation of associated vomiting. Vomiting occurring in babies suffering from the stress of labour or delivery and from cold injury rarely persisted, and then only at irregular intervals, for longer than four or five days, except in the presence of recurrent convulsions. In babies with primary hydrocephalus, congenital heart disease, intestinal obstruction and pyloric stenosis, the duration of vomiting was determined by the length of survival or by the success of operative intervention in appropriate cases. Vomiting arising from difficulties in feeding management ceased on an average within five days, but occasionally persisted for as long as twelve.

Forcefulness. True projectile vomiting was seen in two infants both of whom had pyloric stenosis. Forceful as distinct from projectile vomiting was noted in 50 babies including two with pyloric stenosis, and 12 recovering from intracranial birth stress. The remainder were examples of gastric irritation and/or pylorospasm. Feeding difficulties were accompanied by strong noisy 'windy' vomiting in 18 babies. In no instance did forcible vomiting occur in premature babies or in the presence of systemic infection, major congenital anomalies or metabolic disorders. Vomiting best described as an effortless 'welling up' of stomach contents characterized the two cases of duodenal ulcers, two of the cases with hiatus hernia and three cases of acute intestinal obstruction.

Copiousness. Vomitus of unusually large amount was noted in eight babies with pylorospasm, the two with duodenal ulcers, two with known gastric irritation and two with severe intracranial irritation

TABLE 5

COLOUR OF VOMITUS IN VARYING CLINICAL CIRCUMSTANCES (79 INFANTS)

Colour of Vomitus as Described by Midwife	Clinical Condition
'Faecal'	Intestinal atresia (3)
'Meconium'	Intestinal atresia (4)
Black	Haemorrhagic disease (1) Swallowed meconium (1)
Brown	Duodenal ulcers (2) Swallowed blood (10) Haemorrhagic disease (4) Asphyxia (2) Cold injury (2) Meconium ileus (2)
Red	Haemorrhagic disease (12) Asphyxia (6) Pylorospasm (2) Pyloric stenosis (1) Haemolytic disease (1)
Yellow	Haemolytic disease (3) Foetal distress (3) Asphyxia (2)
Green	Acute obstruction (6) Pylorospasm (2) Septicaemia (3) Congenital heart (3) Asphyxia (4)

associated with severe convulsions. In each instance the vomiting was forceful. None of the infants was premature.

Colour. Unusual coloration of the vomitus was recorded in 79 cases. Relevant observations are summarized in Table 5.

Mucus in Vomitus. Mucus in amounts calling for special comment was present in 200 of the 498 cases in the series. It was constantly absent in certain circumstances and present more consistently in some clinical conditions than in others.

The findings are summarized in Table 6. Excess of mucus in the vomitus was altogether exceptional in babies with acute intestinal obstruction, congenital anomalies of the nervous and cardiovascular systems, metabolic disorders and generalized infections not treated with oral antibiotics or sulphatherapy. By way of contrast among vomiting babies a large amount of mucus was characteristic of the vomitus in over 30% of feeding problems, in 65% of those with pylorospasm and in 60% of those manifesting signs of birth stress.

Among babies in whom difficulties in feeding management occurred, mucus was present in the vomitus of those with choanal atresia, and those who had been overfed, and in a proportion of those experiencing difficulty in changing from human to cow's milk.

Mucus was present in excessive amount in the

TABLE 6

INCIDENCE OF VOMITUS WITH MUCUS IN AMOUNTS PROMPTING SPECIAL COMMENT

Clinical Condition	Number of Babies	
	Vomiting	Vomiting Excess Mucus
Gastro-enteral:		
Difficulties in feeding management	113	35
Gastric disturbance by known irritant	37	6
Pyloric stenosis	4	2
Acute obstruction	17	1
Pylorospasm	43	28
Alimentary infection	7	3
Parenteral:		
Infection	29	3
Developmental anomalies	23	6
Stress of labour and/or delivery	168	105
Unexplained convulsions	2	—
Metabolic disorders	11	—
Cardio-respiratory syndrome	4	2
Hypothermia/cold injury	13	4
Haemolytic disease	19	4
Prematurity	8	1

TABLE 7

VOMITUS IN BABIES WITH CLINICAL EVIDENCE OF BIRTH/DELIVERY STRESS (168 INFANTS)

Evidence of Birth/Delivery Stress	Number of Babies	
	Vomiting	Vomiting Excess Mucus
Foetal distress only	23	21
Foetal distress and delayed onset of respirations	13	10
Foetal distress, delayed onset of respirations and cerebral irritation	15	8
Delayed onset of respirations only	93	57
Intracranial irritation only	24	9

vomitus of 105 of the 168 babies in whom vomiting followed stress of birth or delivery. The cases are analysed in Table 7. Of the 105 babies, delivery of 25 was spontaneous, of 45 instrumental and of 35 by caesarean section. Labour was prolonged in 43 cases. Delivery was precipitate in four and by the breech in 18 cases.

A feature noted in the great majority of infants with a history of foetal distress regardless of the method of delivery and irrespective of whether or not there was post-natal asphyxia or post-natal intracranial irritation, was the extremely viscid tenacious character of the mucus in the vomitus and bucco-pharynx. In these babies the mucus was frequently tinged green. The viscosity of the mucus was such that it could not be sucked out with an extractor and could only be removed digitally.

Incidence of Vomiting

The incidence of vomiting in relation to certain clinical conditions was studied and the results are

TABLE 8

INCIDENCE OF VOMITING IN RELATION TO CERTAIN SELECTED CLINICAL CONDITIONS

Clinical Condition	Number of Cases		% Cases With Vomiting
	Total	With Vomiting	
Acute abdominal obstruction	17*	17	100
Pyelonephritis	9	5	55
Septicaemia with meningitis	7	4	44
Severe infections including septicaemia	18	7	
Haemorrhagic disease	53	17	32
Severe congenital heart disease	41	13	32
Enteritis (? viral)	21	6	28
Stress of labour/delivery	624	168	27
Cold injury/hypothermia	50	13	26
Acute descending respiratory infection	34	7	21
Spina bifida	54	9	17
Maternal diabetes mellitus	45	7	15
Haemolytic disease—			
Exchange transfusion	135	13	9
No transfusion	84	6	
Cardio-respiratory syndrome	60	4	6

* Does not include two babies with meconium peritonitis in whom vomiting commenced postoperatively.

summarized in Table 8. Acute abdominal obstruction was the only condition invariably associated with vomiting. Only one in every three babies with haemorrhagic disease had haematemesis. All infants with spina bifida who suffered from vomiting had associated hydrocephalus or secondary meningitis. As already stated, the cases of enteritis were considered to be of viral origin and differed in the low incidence of vomiting from the more common forms of neonatal gastro-enteritis. A striking feature is the large number of babies in whom vomiting occurred in association with a history of previous foetal or neonatal distress.

Discussion

Incidence. Vomiting if interpreted to include regurgitation is the most common sign encountered in the newly-born. Paterson and McCreary (1956) find that under hospital conditions 80% of infants vomit at least once within 48 hours of birth. Findings in Series A of the present study are in broad agreement with their views. Swenson (1959) expresses the opinion that the tendency of many newborn babies to vomit in small amounts need not cause concern unless the vomitus contains bile. Premature babies are especially prone to vomiting (Dunham, 1955; Swenson, 1959). According to Lundeen and Kunstadter (1958) about 75% of premature infants return food during the first three days of life. The findings in Series A of the present study provide evidence that the tendency is not limited to premature babies, and in Series B that forceful vomiting and copious vomitus are not encountered in premature infants.

Aetiology. Vomiting in the newborn may be due to a specific cause or it may be evidence of general systemic disease. On the other hand it may result from no more than transient difficulty in making adjustments necessary for the establishment of a separate existence. Series B indicates the wide variety of circumstances in which vomiting occurs (Table 4). Nevertheless, acute abdominal obstruction was the only condition invariably associated with vomiting (Table 8).

The large number of cases in which vomiting occurred in association with a history of foetal or neonatal distress (Table 8) has to be seen in perspective. It reflects the frequency with which foetal distress and post-natal asphyxia occur in obstetrical practice. Although considerable, the incidence of vomiting in these cases is less than that occurring in the presence of infections.

There is general agreement that regurgitation and vomiting in the newborn may be due to errors or difficulties in feeding management, fluid and other material swallowed during delivery, infection, or an intracranial lesion. Nelson (1959) considers that overfeeding and failure to promote eructation of swallowed air are relatively frequent causes of vomiting, and Dunham (1955) attaches importance to oral feeds given too rapidly or in too large amounts to premature babies. The present study confirms the importance of wind swallowing as a cause of vomiting. Two groups of infants were of particular practical importance. There were the infants in whom excessive wind swallowing with consequent vomiting resulted from persistent efforts to get the baby to fix at breasts with minimal milk secretion; and the disinterested dyspeptic babies who vomited following injudicious persistence in attempts to give oral feeds. It is not without significance that the vomitus of babies in the second group contained large amounts of mucus.

Foreign material in the stomach stimulates vomiting. The relationship between vomiting and blood in the stomach from whatever source is clearly established. An equally clear relationship exists between vomiting and swallowed meconium and maternal secretions. It cannot be maintained that a comparable relationship between vomiting and swallowed amniotic fluid has been proved. The presence of liquor amnii in vomitus cannot be detected by naked eye examination. Furthermore, there is the view advanced by Hughes (1952) that amniotic fluid is probably non-irritative.

The amount of mucus in the vomitus prompted special comment in over 40% of babies in Series B (Table 6). The question arises as to whether the apparent excess of mucus should be regarded as

abnormal. In my opinion excess mucus in the stomach is evidence of functional abnormality. It is not uncommon for a baby to vomit before oral feeding has commenced, or for an isolated vomit to take place at or shortly after the time of a baby's first feed. The vomitus often contains mucus. Pylorospasm exemplifies the other extreme, recurrent vomiting persisting until excess secretion by the gastric mucosa ceases (Craig, 1955). Between these extremes is the case of the dyspeptic baby, who is disinclined for feeds and reacts to 'forced feeding' by vomiting mucus. The results of gastric lavage before feeding of these infants contain a considerable amount of mucus. Lavage is as successful in dispelling anorexia in these infants as it is in arresting vomiting in babies with pylorospasm. Common to the various disturbances mentioned is the establishment of normal alimentary digestive and mechanical function by removal of excess mucus.

If it be accepted that excess gastric mucus secretion is evidence of functional disturbance—is the excess mucus the primary source of gastric disturbance or is it evidence of gastric reaction to some irritant? In the present study excess of mucus was rarely found in the presence of such obvious gastric irritants as blood, meconium or post-nasal secretion. This is probably accounted for by the promptitude and effectiveness with which vomiting expels such substances. I can offer no explanation for the excess mucus present in infants with pylorospasm and in a proportion of the infants vomiting as a result of feeding difficulties. There were no abnormal curds in the vomitus or motions of these babies to suggest difficulty in digestion. The possibility of torsion of the stomach (Eek and Hagelsteen, 1958) was considered, but in the few cases submitted to radiological examination there was no evidence to suggest that diagnosis.

Of particular interest is the presence of excessive mucus in 60% of the babies in whom vomiting occurred against a background of abnormal antenatal or natal stress. To some extent the finding is at variance with Westin's (1958) conclusion that the amount of gastric contents in the foetus is not influenced by asphyxia. The analysis in Table 7 suggests that the association applies particularly to foetal distress and post-natal asphyxia separately or in combination, and to a lesser extent to intracranial disturbance not preceded by detectable intrauterine or immediate post-natal anoxia. An incidental finding was that excess mucus was not a feature of the small number of babies with neonatal asphyxia attributable to narcotics administered to the mother. The extreme viscosity of the mucus vomited by babies with a history of foetal distress was not a feature of any other condition, although mucus in the vomitus of infants with hyaline membrane disease was more tenacious than that seen in cases of pylorospasm or feeding difficulties.

The extent to which increased intracranial pressure or gastric irritation is the more important factor contributing to vomiting in cases of birth stress is debatable. It can be said, however, that increased intracranial pressure accounted for the vomiting in infants with massive intracranial haemorrhage, subdural effusions, hydrocephalus complicating spina bifida, and septicaemia culminating in meningitis. A similar explanation may apply to infants with cold injury in whom cerebral oedema sometimes develops. Among babies with haemolytic disease vomiting occurred in a proportion of those who were untreated and of those given an exchange transfusion, and was probably attributable to more than one cause.

Obstruction. The finding of only four cases of pyloric stenosis is not surprising. The condition is rarely encountered in the first 10 days of life (Holt and McIntosh, 1953; Nelson, 1959; Dunham, 1955) and a number of writers make no mention of it as a possible cause of vomiting in the newly-born.

Acute obstruction accounted for the vomiting in 17 of the 498 cases in Series B. Diaphragmatic hernia is given as a cause of vomiting by Dunham (1955), Nelson (1959) and Hughes (1952). Immediate regurgitation is mentioned by Nelson (1959), and Holt and McIntosh (1953) as of importance in the recognition of oesophageal atresia. During the period of the present study a diagnosis of diaphragmatic hernia was confirmed in six infants in whom vomiting did not occur, and five babies with oesophageal atresia were diagnosed and operated on before being given oral feeds and in the absence of vomiting.

Many statements appear in the literature concerning the significance of coloured vomitus. Holt and McIntosh (1953) consider that bile-stained vomitus is usually evidence of atresia of the bowel. According to Hughes (1952), Weiner and Richmond (1950), Paterson and McCreary (1956) and Nelson (1959) persistent bile-stained vomiting, especially if accompanied by abdominal distension, is strongly suggestive of atresia below the level of the ampulla of Vater. Glover and Barry (1949) stress that the absence of bile from vomitus does not exclude obstruction as atresia can occur above the level of the ampulla, but Ladd and Gross (1941) are of the opinion that because atresia occurs only very rarely above this level, it is almost always associated

with bile-stained vomitus. Swenson (1959) expresses the view that small premature babies sometimes vomit bile in the absence of intra-abdominal disease.

While these generalizations have substance they can be a source of unnecessary anxiety if applied too arbitrarily and without regard to the inevitable variations in individual observations on the colour and other characteristics of vomitus. There is evidence of this in Table 5. Green or yellow vomitus was recorded in no fewer than 26 cases, but was attributable to obstruction in only six. Faecal and meconium vomitus are diagnostic and *dark* green vomitus is virtually diagnostic of obstruction. Interpretation of the significance of other variations in colour requires study of other characteristics of the vomiting together with observations concerning the presence of distension, respiratory embarrassment resulting from pressure on the diaphragm and an anxious facies expressive of pain. Dehydration of any considerable degree is rarely detectable in the early stages. I cannot agree with the statement (Glover and Barry, 1949) that visible peristalsis a few days after birth almost always indicates congenital obstruction in the upper intestinal tract. Peristalsis is a feature of many healthy premature babies, of feeding problems associated with wind swallowing and of pylorospasm.

The absence of cornified epithelial cells and lanugo in the stools during the first 48 hours of life is not conclusive evidence of obstruction nor is the passage of a small meconium stool conclusive of patency of the alimentary tract. Detection of excessive intestinal peristalsis by auscultation is of diagnostic value. Radiological examination can confirm suspicions of intestinal obstruction by demonstrating absence of air in the rectum in the presence of distended small intestine with fluid levels. Ladd and Gross (1941) advocate radiological examination whenever vomiting continues for the first day or two of life in a baby receiving suitable feeds. Nevertheless, the total clinical picture of the baby considered in relation to age, maturity and feeding is of prime importance in assessing the significance of vomiting in most cases. Swenson (1959) attaches particular importance to the appearance of the infant. In his opinion deviations in appearance, although difficult to describe, are often of greater assistance than abdominal examination in appraising the status of intestine involved in obstruction.

A tentative diagnosis of intestinal obstruction can occasionally be made before the occurrence of vomiting. This applied to two babies not included in the present series in both of whom extreme abdominal distension, abdominal facies and inertia gave rise to anxiety within a few hours of birth. Vomiting was postoperative. Both cases were examples of meconium peritonitis and both survived. Neither infant received oral fluids before operation.

With regard to the less common alimentary anomalies causing vomiting, Astley and Carré (1954) state that large amounts of blood and mucus are present in the vomitus of infants with gastro-oesophageal incompetence. This was not a feature of any of the four cases in my series. Discussing duodenal ulcers, Holt and McIntosh consider that melaena is usually the first sign and that vomiting is often absent. Swenson (1959) describes haematemesis as suggestive of duodenal ulcer, more especially if bleeding is profuse or persistent. In two cases previously reported by me, melaena was present in one in the absence of vomiting and in the other there was persistent vomiting and increasing pallor but no visible haemorrhage (Craig, 1934). Vomiting occurred in the two cases in the present series and diagnosis during life was aided by the way in which copious amounts of blood welled up from the stomach.

This study illustrates the infinite variety of clinical problems inseparable from vomiting in the newborn. The diagnostic challenge to the surgeon differs greatly from that with which the physician is faced. Of newborn babies referred to the general surgeon on account of vomiting, the majority are suffering from some form of partial or complete obstruction of the alimentary tract. The maternity hospital physician probably sees as many examples of alimentary obstruction as his surgical colleague, but to the physician obstruction is a relative rarity compared with other conditions giving rise to vomiting in the newborn. In this study the 17 cases of intestinal obstruction represented between 3 and 4% of babies reported as vomiting, and about 10% of infants whose vomiting gave rise to particular anxiety on account of urgency or uncertain diagnosis. The term 'infrequent yet serious disease' with all its implications described by Spence, Walton, Miller and Court (1954) can be aptly applied to obstruction in the newborn. The physician's task remains to differentiate the causes of vomiting which to quote Still (1927) 'sometimes is mere physiological riddance, sometimes the first indication of grave or even fatal disease'.

Summary

A clinical study of vomiting in the newborn is described.

Vomiting occurred in the first week of life in 65% of 273 healthy babies of whom 26 were premature and 247 were born at term or after.

Neonatal vomiting noted in 498 ailing infants was associated with gastro-enteral conditions in 221 and with parenteral conditions in 277. Of the 498 babies, 109 were premature.

Forceful vomiting and copious vomitus were not encountered in premature infants.

In no case was vomiting attributable to milk allergy.

Mucus in amounts calling for special comment was a feature of the vomitus in 200 ailing infants being noted in 30% of feeding management problems, 65% of infants with pylorospasm and 60% of those with evidence of birth stress.

Viscid tenacious mucus was characteristic of the vomitus in the majority of babies with a history of foetal distress.

Aetiology is discussed. Doubt is expressed as to whether swallowed liquor amnii is a common cause of vomiting. It is suggested that the presence of excess mucus is evidence of functional disturbance and a frequent cause of vomiting.

Abdominal obstruction was the only condition constantly associated with vomiting.

Faecal and meconium vomitus are diagnostic and *dark* green vomitus is virtually diagnostic of obstruction. Other variations in the colour of vomitus have no constant diagnostic significance.

The total clinical picture including the clinical appearance of the infant is of prime importance in the diagnosis of obstruction.

I am indebted to a number of colleagues for assistance. At the Leeds Maternity Hospital senior obstetrical staff gave every facility for the study, and Dr. M. E. Coles, Miss M. Pattullo, S.R.N., S.C.M., Sister P. White and Sister E. Oliver co-operated in the making and recording of clinical observations. Additional valuable help was received from Dr. J. M. Littlewood and Miss E. M. Bond of the University Department, and from Dr. W. Goldie, St. James's Hospital, Leeds.

References

Astley, R. and Carré, I. J. (1954). Gastro-oesophageal incompetence in children: with special reference to minor degrees of partial thoracic stomach. *Radiology*, **62**, 351.

Craig, W. S. (1934). Duodenal ulcers in the new born. *Arch. Dis. Childh.*, **9**, 57.

—— (1955). Palpable contractile pyloric tumours in the newly born. *Ibid.*, **30**, 484.

Dunham, E. C. (1955). *Premature Infants*. Cassell, London.

Eek, S. and Hagelsteen, H. (1958). Torsion of the stomach as a cause of vomiting in infancy. *Lancet*, **1**, 26.

Glover, D. M. and Barry, F. McA. (1949). Intestinal obstruction in the newborn. *Ann. Surg.*, **130**, 480.

Holt, L. E., Jr. and McIntosh, R. (1953). *Pediatrics*, 12th ed. Appleton-Century-Crofts, New York.

Hughes, J. G. (1952). *Pediatrics in General Practice*. McGraw-Hill, New York.

Ladd, W. E. and Gross, R. E. (1941). *Abdominal Surgery of Infancy and Childhood*. Saunders, Philadelphia.

Lundeen, E. C. and Kunstadter, R. H. (1958). *Care of the Premature Infant*. Pitman Medical Publishing Co., London.

Nelson, W. E. (1959). *Textbook of Pediatrics*, 7th ed. Saunders, Philadelphia.

Paterson, D. and McCreary, J. F. (1956). *Pediatrics*. Lippincott, Philadelphia.

Spence, J., Walton, W. S., Miller, F. J. W. and Court, S. D. M. (1954). *A Thousand Families in Newcastle upon Tyne*. Oxford University Press, London.

Still, G. F. (1927). *Common Disorders and Diseases of Childhood*, 5th ed. Oxford University Press, London.

Swenson, O. (1959). *Pediatric Surgery*. Staples Press, London.

Weiner, L. R. and Richmond, J. B. (1950). The diagnosis of surgical conditions of the newborn infant. *J. Pediat.*, **36**, 107.

Westin, B. (1958). On the amount of gastric contents in the normal and the asphyxiated newborn infant. *Acta paediat. (Uppsala)*, **47**, 354

BOOK REVIEWS

Report of the Heights and Weights (and Other Measurements) of School Pupils in the County of London in 1959. By J. SCOTT. (Pp. viii+247; 18 figures+63 tables. 39 NF.) London County Council. 1961.

The London County Council's periodic five-year surveys of children's heights and weights have become established as a major source of normal figures for this country and the Council's latest survey, made in 1959 and reported here, establishes it even more firmly as the leading authority in this field. This time not only were height and weight taken but also two measurements of subcutaneous fat, by the skinfold caliper technique, and measurements of upper-arm and calf circumference. In the interests of accuracy the old method of having many different people measuring for the various schools was dropped, and teams of two health visitors per Division were selected, briefed and given a number of training sessions in the Department of Growth and Development at the Institute of Child Health.

As on previous occasions a random sample of schools was taken from each of the nine Divisional Areas and a total of 25,000 boys and girls was measured, being approximately 1,000 of each sex each year from 5-14 inclusive, with half this number of 15-year-olds, a quarter this number of 16-year-olds and a few 4-year-olds. As before the results are presented as frequency distributions of height and weight, with 3rd, 10th, 25th, 50th, 75th, 90th and 97th percentiles at each year of age: the same has been done for the newly-added measurements. There is also a number of Tables of bivariate distributions, irrespective of age, including notably the distributions of weight according to height, according to arm circumference, calf circumference and subscapular skinfold.

The results show that London children were taller and heavier in 1959 than in 1954, though this time only at ages over 8. Evidently the secular trend is still operating at adolescence—14-year-old boys having increased 2 cm. during the past five years and 12-year-old girls having increased 1·7 cm.; but it does seem as though the trend is stopping in the pre-school years. Further data on this aspect will be awaited with much interest.

Each girl was questioned as to whether or not she had begun to menstruate and the average time of menarche was calculated from this by the method of probits; the average age in 1959 was 13·05 years, which is three months earlier than in 1954. Thus, the secular trend in this measure of maturity, estimated by Tanner to have been about four months per decade over the past 60 years, has been well maintained.

Children in different health Divisions of the County differ now by less than 2% at any age. This survey provides new and valuable data on the relation between height and weight and the number of brothers and sisters in the family, confirming for London what was well established some years ago by Scottish data that there is a considerable decrease in size in children from larger families. Nine-year-old boys, for example, are 5 cm. shorter when they possess four or more siblings than when they are only children. This differential is seen at all ages and it is the greatest pity that the London County Council was unable to report the occupational/social class of the families and thus to see how much the family size effect was characteristic only of the families with lower incomes, as in the Scottish data. This omission is indeed a glaring fault of the otherwise most excellent and comprehensive survey. Surely one of the major reasons for such a survey is to see whether the children of the less economically favoured members of the community are growing as well as those of the more economically favoured, and this the survey fails to do. Where the London County Council is most to be congratulated is on having included for the first time data on body fat and on family size, both of which are of much interest to paediatricians, nutritionists and others concerned with growth. It is to be hoped that in 1964 it will take a further important step and obtain data on social class.

Child Guidance Centres [Wld Hlth Org. Monograph Ser. No. 40]. By D. BUCKLE and S. LEBOVICI. Pp. 133. 20s.) London: H.M.S.O.; Geneva: World Health Organization. 1960.

This monograph describes the functions of child guidance centres, and their relationship to the social services; it is based on lectures and discussions held at a Seminar which took place in Lausanne in 1956. It repays careful study, as it is full of useful information based on experience. Subjects include location and equipment of the clinic, qualifications of the members of the child guidance team, techniques of case finding, history-taking, and diagnosis and treatment of behaviour disorders of children.

The chapter on the child guidance team discusses the training and the functions of the social worker, the educational psychologist, and the psychiatrist. In theory, the psychiatric social worker is mainly concerned with the parents and with the case history; the educational psychologist assesses the child's mental abilities, and the psychiatrist makes the final diagnosis, and institutes treatment. Case conferences are held by these three members of the team and individual children are discussed; other interested persons may be invited to be present. This is the familiar pattern of the child guidance set-up, but such arrangements do not always prove satisfactory. The importance of the team working harmoniously together, and the harm done by internal dissensions within the group are admitted and discussed.

It is suggested that in some cases members of the team might profit from personal analysis. They should have healthy and balanced personalities, a breadth of vision, and their emotional and family lives should be stable.

The location of the clinic is discussed in some detail.

Child guidance centres have developed differently from traditional medical clinics, because the total environment of the child needs to be considered. The writers consider that the child guidance centre is an agency for improving the adjustment of children, with special reference to social and emotional relationships. Children are to be helped to adapt themselves to their circumstances. Moreover, the modern conception of the Child Guidance Clinic is, that it is not only the child, but the whole family, that needs to be treated. For this reason, it should form an essential part of the social and medical services. The number of children with psychiatric disorders is small and they should be treated in hospital. The Report suggests that if a new centre is being planned, it is better, because some children are afraid of hospitals, to avoid placing it in one. The convenience of having some kind of a mental hygiene unit in the children's hospital, where paediatricians can collaborate with the psychiatrist is, however, stressed. It would be undesirable for child guidance and child psychiatry to be considered as a sub-branch of paediatrics, for the work involved goes far beyond the traditional field of medicine, and calls for non-medical skills.

There is a most interesting chapter on the technique of psycho-analysis of children between 6 and 10, and a useful classification of disorders is given. The appendix 'Annex 1' contains an account of the effective development of the child, in which psycho-analytic data is integrated into the neurobiological study of the child.

This monograph is well worth reading, not only by those working in the field, but also by those who wonder what purpose the child guidance centres serve.

Orthopaedics. By GEORGE PERKINS. (Pp. xiii+975; 577 figures. 126s.) London: The Athlone Press. 1961.

I enjoyed reading this book very much, it is well conceived, the text is clear and easy to read. The illustrations are well done and lavish in number. The x-ray illustrations in particular demonstrate basic principles and detailed rarities with equal clarity. I found the enlargements of small framed areas in these x-ray illustrations of great value. One minor criticism is that the text in the early chapters tends to outrun the illustrated page, but this is perhaps unavoidable and is no doubt a printing difficulty, insurmountable in a book of this size.

The chapter on examination is good. It puts in simple uncluttered language all the essential basic principles of an adequate examination of an orthopaedic case and, as is so necessary in this day and age, the paragraph dealing with x-ray examination is extensive.

The bone dystrophies are well handled and fully covered with the minimum of controversy, good illustration and simple description without confusion by the inclusion of many and varied descriptions.

A comment rather than a complaint on this, and the chapter on vascular disease from a paediatric point of view, is that many diseases are well known to a paediatrician under the name of the original medico describing the condition, e.g. Legg-Perthes disease is a term better known to the paediatrician than pseudo-coxalgia. I could not discover the name Legg-Perthes disease in the index under either Legg or Perthe, although Legg is mentioned in the text; Köhler and Freiberg's disease are indexed and adequately covered in the text and are described separately under osteochondritis of the scaphoid and metatarsal, but osteochondritis of the hip is not indexed. Fanconi syndrome, Morquio's disease and Hand-Schüller-Christian disease are indexed and described, but gargoylism is neither mentioned nor indexed.

The congenital deformities described under 'errors of segmentation' might have had a small paragraph included under treatment of the lower limbs to include platform prostheses.

Dislocation of the hip and talipes equino-varus are fully covered, although at certain centres the treatment advised would be frowned upon. I cannot agree that illustration 395 is Denis Browne's splint for talipes equino-varus—it is one of many, and this one in particular was abandoned some years ago and at that time it was used to hold a corrected talipes equino-varus after manipulation.

This is an excellent book and should be in all medical libraries and orthopaedic surgeon's bookshelves; it also offers virtual full coverage to that specialized corner paediatric orthopaedics.

Differentialdiagnose von Krankheitssymptomen bei Kindern und Jugendlichen, Vol. I. By WERNER CATEL. (Pp. xxxvi + 1051; 483 figures + 70 tables. DM. 220.) Stuttgart: Georg Thieme. 1961.

The first volume of this truly epic trilogy deals with disorders of bones and joints, the haemopoietic system and metabolic diseases. A vast amount of ground is covered in great detail with meticulous thoroughness. The wealth of information given makes the work a reference book for postgraduates rather than a textbook for undergraduates. A good system of headings, sub-headings and paragraphs, numerous comprehensive and clear tables and many excellent photographs and radiographs make the material presented easy to read and absorb. Many of the conditions described are further illustrated by short succinct case summaries. Details of laboratory technique are given where appropriate. As is implied in the title, the author and collaborators have not regarded treatment as being within the scope of this book. This is a pity, as most clinicians would probably prefer to read about treatment and management in a book of this size and price than about standard laboratory techniques. Each chapter is followed by an extensive bibliography of the international

literature on each subject and modern British and American views are given due prominence. The approach to clinical paediatrics as a whole is thoroughly modern and up to date. It is gratifying to see that the gulf which has separated the German and Anglo-American paediatric thinking in the post-war years seems to be getting narrower. We must welcome this excellent monumental work, which will find a permanent place not only in German-speaking countries but on the shelves of all paediatric libraries. We look forward to the appearance of the other two volumes.

The Healthy Child. Edited by HAROLD C. STUART and DANE G. PRUGH. (Pp. xvi + 507; 6 figures + 4 tables. 80s.) Cambridge, Mass: Harvard University Press; London: Oxford University Press. 1960.

This book, edited by an emeritus professor of maternal and child health and an associate professor of paediatrics and psychiatry, is a forward-looking book, at least in its attempts to achieve a grouping together of knowledge and ideas of physiology, sociology, mental health, maternal health, growth and development, mental growth, and a host of other items which may be regarded as central or marginal in all those considerations significant in the 'close and important tie between health and development'. In broad terms this book presents a picture of the child and his expected progress at all ages 'from conception to maturity'. It is intended for professionals and is stated to provide a background essential for workers in the fields of education, psychology, nutrition, social work, nursing, public health and medicine.

Undoubtedly a great deal of easy and comfortable reading exists in this book and most of the 20 contributors have given a balanced emphasis sufficient to indicate to 'professionals' (social workers, psychologists, and others) the many factors involved in obtaining and maintaining health in children. We can give the book good recommendation for its general form and apt chapter sequences, extensive bibliography and up-to-date references. In the United Kingdom this volume might well have its maximum usefulness in the new three-year training course for teachers or as a means of adding strength to health education programmes. Paediatricians would also find something acceptable and here and there a new idea to add to their 'health mindedness' in everyday practice.

A Synopsis of Children's Diseases. 3rd ed. By JOHN RENDLE-SHORT. (Pp. xii+660; 15 figures+25 tables +3 appendices. 42s.) Bristol: John Wright. 1961.

This is a book of the synopsis type which is not intended to take the place of standard textbooks. It concentrates into the short space of 600 pages the basic facts about all the major diseases of children. To read and digest its entire contents would give the most hardened examination candidate dyspepsia and its real value is doubtless to fill the gaps in his knowledge, and as a convenient source of reference. To accomplish these purposes a book should be both comprehensive and reliable and this new edition rates highly on both scores. There are few omissions of any importance, although a chapter on the adenoviruses would have improved the section on viral diseases and the book does not reflect current interest in resistant rickets and the chemotherapy of primary tuberculosis. The introduction of the metric system has enhanced the usefulness of the book and has been accomplished with few errors apart from the electrifying statement that a baby gains 440 g. per day for the first 100 days! The new section on electrocardiography is informative and well balanced.

It is probably inevitable that such a book should be dogmatic at times, but herein lies a danger, for although dogma may be recognized by the experienced, it will readily mislead the inexpert reader for whom the book is intended. Thus comments, that exchange transfusion is required if bilirubin exceeds 18 mg. % in prematurity, that the lingual fraenum is never short enough to cause trouble, and that it is essential to locate the vein before intravenous transfusion need expansion before they are wholly acceptable. When space has precluded the proper appraisal of a topic, it would have been better to omit it, for brief references such as those to selenium in teratogenesis and to steroids in the treatment of the wheezy child are misleading and may even be dangerous. With these slight reservations, Rendle-Short's book can be confidently recommended and the fact that a third edition has been required already is evidence that it satisfies a need.

Experiences with Congenital Biliary Atresia. By JULIAN A. STERLING. American Lecture Series. (Pp. ix + 68; 21 figures; 3 tables. 45s.) Springfield, Illinois: Charles C. Thomas; Oxford: Blackwell Scientific Publications. 1960.

The author of this monograph disarms criticism by stating that he will restrict it to a clinical account of the management of 10 cases of atresia of the bile ducts. Opinions may differ as to the value of making such a report in book form.

The operation of bouginage of the liver and attachment of intestine to the portal region in the hope of draining 'bile lakes' is an old one. Dr. Sterling has brought it up to date using silver tubes in the liver and reports a successful case followed for two years. There is an addendum to the book of one sentence which notes that eight cases have now been successfully treated by the same operation. It would be foolish to disregard any method giving therapeutic hope in this difficult condition, but another edition reporting these eight cases in detail would carry more weight.

Virus Meningo-encephalitis. Ciba Foundation Study Group No. 7 (Editors: G. E. W. WOLSTENHOLME and MARGARET CAMERON). (Pp. viii+120; 11 figures. 12s. 6d.) London: Churchill. 1961.

Clinicians, virologists and pathologists are equally concerned with an ever-increasing variety of virus meningo-encephalitis. This report of discussions by a group of experts makes it evident that the variety of

viruses which are known may become neurotropic is steadily increasing, and that the possibilities of accurate diagnosis depend more and more on the virus laboratory. Thus, for the entero viruses Dr. Scherer advises that in order to isolate the virus the clinician should take gargles of 10-15 ml., specimens of faeces and of C.S.F. on three consecutive days and get them to the laboratory as fast as possible. Sero-diagnosis, unfortunately, presents problems since these are now 25 ECHO, 20 Coxsackie and three polio viruses. We clearly need more special units to study these infections, for the laboratory tests, though obviously deserving of special research, are as yet of little assistance to the clinician in charge of the patient. In this connexion the Virus Laboratory in Glasgow is taking a valuable lead and some of their recent work was reported to this conference by Dr. N. R. Grist.

The Natural History of Cerebral Palsy. By BRONSON CROTHERS and RICHMOND S. PAINE. (Pp. 299; 66 figures + 37 tables. 32s. 6d.) Cambridge, Mass.: Harvard University Press; London: Oxford University Press. 1959.

With some honourable exceptions, such as the early works of Sigmund Freud, the literature on so-called cerebral palsy must be about the most confusing and least satisfactory in the whole field of medicine. It abounds in bewildering classifications, uncontrolled observations about aetiology, clinical descriptions couched in esoteric and incomprehensible terms, and dogmatic and unverifiable assertions about therapy. This book is refreshingly different. It is based on a unique study of the childhood, and in many cases the early adult life, of some 1,800 victims of cerebral palsy who were seen between 1930 and 1950; 750 of these patients were re-examined and the remainder contacted by letter. The analysis of the lives of these children is accompanied by a careful and thorough commentary on the literature. It is clear from the very different styles that each chapter was mainly written by the one or other author. Dr. Crothers' contributions are philosophical in content and almost conversational in style; Dr. Paine's are more conventional, concise and factual, and much of the information is presented in the form of tables. Each supplements the other admirably.

The whole subject of the cerebral palsies is dealt with in this book. There are chapters on growth and development, examination, clinics for cerebral palsy, clinical studies of the various types, electroencephalography, intelligence and education, life expectancy and employability, treatment, and the effect on the family. But perhaps the main concern of the authors, as the title of the book implies, has been to explain and illustrate the ways in which the relevant types of brain disorder affect growth and development. This is, after all, the essence of paediatrics, and the respect in which it differs from other branches of medicine, and this book provides a model which should be studied by writers on other aspects of paediatrics.

To quote Dr. Crothers: 'The pleasures and the difficulties of the supervision of young children are largely concerned with controlling behaviour without impairing initiative.' 'The presence of a distortion of development upsets the timing of the relation between the child and those who have authority over it.' This has an important bearing upon the controversial matter of physical therapy. 'On one side are directors who believe fully that the core of the whole problem is intensive, prolonged physical therapy. On the opposite side are men who feel that the important matter is the fostering of growth and development and the achievement of as much independence as is consistent with the disability.' 'Perhaps one way of describing the two extremes is to suggest that one side relies on their ability to bring up children while the other tries to facilitate growing up and to keep their hands off as far as they can.' The authors admit that they are unable to appraise therapy accurately, but they conclude that physical treatment is reasonably satisfactory in patients with spasticity and ineffective in the 'extra-pyramidal' group. One of the most interesting chapters in this book concerns the emotional status of cerebral palsy patients in adolescence and early adult life. It is illustrated by numerous case histories and the important conclusions made by the authors are as follows: In the extra-pyramidal group there is no specific type of emotional disorder, although many of the patients were disturbed and sometimes bitter and resentful. In contrast, in the pyramidal cases, a typical disturbance occurred when the patients were subjected to incessant pressure. This took the form of the catastrophic reaction described by Kurt Goldstein, consisting of complete withdrawal to a simpler kind of existence.

This is a medical work of great importance; it is written with authority and modesty. The book, imbued with his high intelligence, compassion and humour, is a fitting memorial to the late Dr. Bronson Crothers' professional life, and it is a work in which his younger colleague must be proud to have played an important part.

The Newborn Child. By DAVID G. VULLIAMY. (Pp. vii +163; 34 figures. 15s.) London: Churchill. 1961.

The care of the newborn has improved out of all recognition during the past 10 years, and in many ways has increased greatly in complexity. Nevertheless, the age-old principles of good antenatal care and obstetrics, the successful establishment of respiration, the satisfactory establishment of breast-feeding, or failing that a suitable alternative, care of the premature and the minimum of prevention remain, and in many ways have become simpler and more rational as the understanding of physiology and pathology of the newborn has grown.

Dr. Vulliamy has written a useful little book which, although it remains simple and easily understood by everybody, nevertheless very adequately covers the recent advances that have been made. The book is addressed to students and nurses, and will certainly be widely used by them, but is also suitable as a standby for the family doctor.

The arrangement is lucid and carefully paragraphed, the printing, paper and binding are excellent, and perhaps

only the illustrations chosen are at random and inadequate in number. Probably the author was anxious to keep down the price. There is no other book that covers the field in quite this way, and it deserves a wide success.

Artificial Feeding in Early Infancy. By ANDREW BOGDAN. [Tutorial System Publications—Paediatric Series.] (Pp. 24. 3s. 6d.) Leeds: Austick's Medical Bookshop. 1961.

There is a great deal to be said, from the student's point of view, for a cheap paper-backed pamphlet which underlines the main problems of any subject. There is still more to be said for one which includes a large number of empty pages on which he can note his own observations from the pearls picked up from his teachers. This little book admirably fulfils these requirements.

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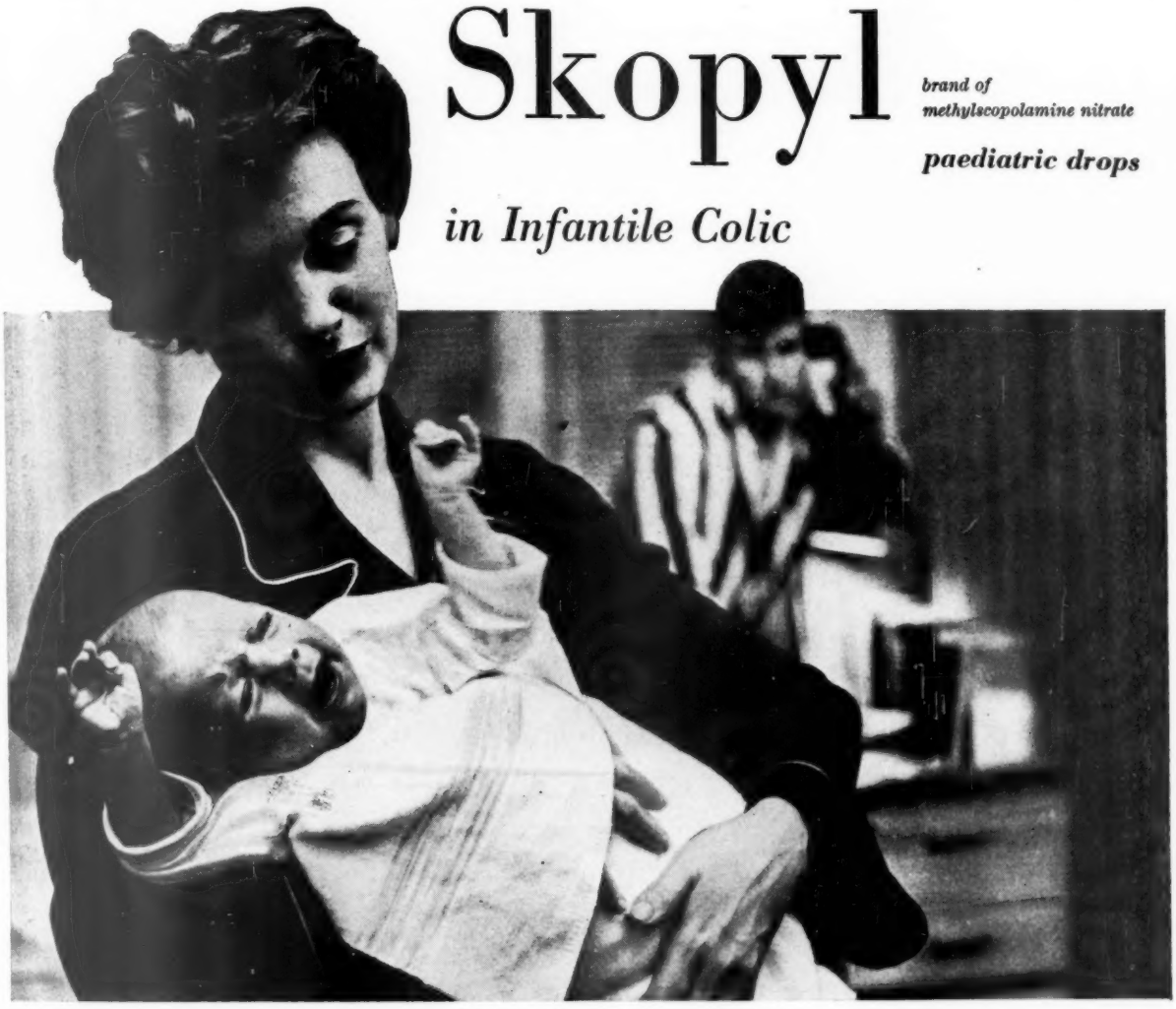

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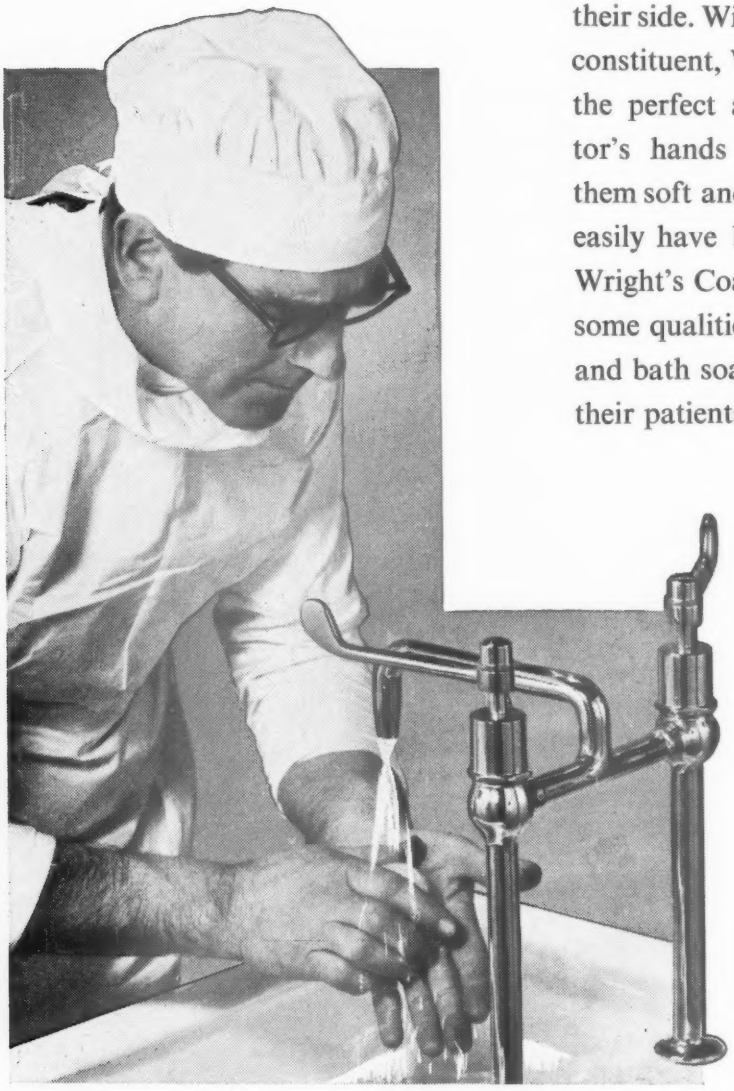

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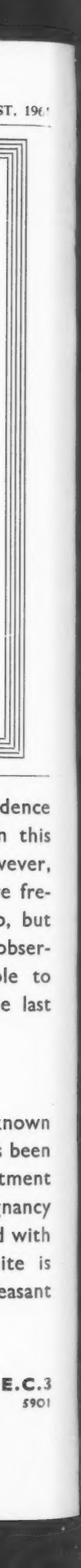

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